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INVOLVEMENT OF THE NERVOUS SYSTEM ASSOCIATED WITH ENDOCARDITIS

NEUROPSYCHIATRIC AND NEUROPATHOLOGIC OBSERVATIONS IN FORTY-TWO CASES OF FATAL OUTCOME

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The neurologic and psychiatric complications of endocarditis are rather well known, but awareness of the high incidence of neuropathologic changes and the effort to surmise their existence on clinical evidence seem to be lacking. The various types of endocarditis have been delineated, and it appears that they may be correlated with the various types of encephalic injury. Additional clinical observation will be necessary before it can be decided to what extent dominant neuropsychiatric traits may be similarly correlated.

NEUROPSYCHIATRIC DISORDERS ASSOCIATED WITH ACUTE ARTICULAR RHEUMATISM AND WITH CHOREA

It is well known that acute simple endocarditis, or rheumatic endocarditis, and acute articular rheumatism are closely related. Cerebral involvement with the latter disease was said in the middle of the nineteenth century to have occurred in about 4.8 per cent of cases and to have had almost always a fatal termination. If the acute articular rheumatism is otherwise uncomplicated, the association of neurologic disorders of such severity is now much less frequent.[1] Hemiplegic attacks have been described, and when they were of short duration the observers attributed them to arterial spasm resulting from the action

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1. Gottsegen, G.: Zerebrale Störungen im Verlaufe des akuten Gelenkrheumatismus, Schweiz. med. Wchnschr. **65**:280-281 (March 23) 1935.

of toxins or viruses.[2] Subarachnoid hemorrhage may occur and need not always end fatally.[3] Chorea, chorea insaniens associated with a fixed downward deviation of the ocular globes, muscular twitching,[4] rhythmic myoclonus of isolated muscles that reminds one of the myoclonic manifestations often observed with epidemic encephalitis,[5] polyneuritis[6] and pyramidal and extrapyramidal rigidity have been described.[4] Mental symptoms of acute articular rheumatism include delirium, motor agitation,[7] hallucinations, delusions,[4] typhoid states,[3b] lethargy and coma.[4] Those of chorea include irritability, emotional lability, lack of concentration and, less frequently, depression, delirium, mania, hallucinations and delusions.

In cases of chorea minor most of the pathologic studies have been directed to the lesions in the basal nuclei,[8] especially the caudate and lenticular nuclei. Several workers have described lesions in the cortex,

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2. Froment, R., and Brun, J: Myoclonies survenues au dècours d'une crise de rhumatisme articulaire aigu. Encephalite rhumatismale "a minima" (présentation de maladie), Lyon méd. **157**:687-690 (June 7) 1936. Germain, A., and Morvan, A.: Angiospasme cérébral au cours d'une maladie rhumatismale, Bull. et mém. Soc. méd. d. hôp. de Paris **53**:551-553 (April 23) 1937.

3. (*a*) Plazy and Marçon: Hémorrhagie méningée au cours d'un rhumatisme articulaire aigu, Bull. et mém. Soc. méd. d. hôp. de Paris **52**:1540-1542 (Nov. 22) 1928. (*b*) Sharpe, F. A.: Subarachnoid Haemorrhage Probably Due to Rheumatic Infection, Brit. M. J. **2**:582 (Sept. 28) 1929.

4. Winkelman, N. W., and Eckel, J. L.: The Brain in Acute Rheumatic Fever; Nonsuppurative Meningo-Encephalitis Rheumatica, Arch. Neurol. & Psychiat. **28**:844-870 (Oct.) 1932.

5. Simmonds, M.: Ueber Hirnblutung bei verrukoser Endocarditis, Deutsche med. Wchnschr. **27**:353-356 (May 30) 1901.

6. Bouchut, L.; Froment, R., and Badinand, L.: Polynévrite, première manifestation d'un rhumatisme viscéral solitaire, Lyon méd. **157**:472-473 (April 19) 1936.

7. Frisch, I. A.: Rheumatic Encephalitis (Chorea Insaniens): A Case Report with the Use of Avertin Therapy, J. Pediat. **5**:654-658 (Nov.) 1934. Telgmann, J.: Toxämische Delirien bei Herzkranken, Deutsche med. Wchnschr. **25**:305-307 (May 11) 1899.

8. (*a*) Bodechtel, G.: Gehirnveränderungen bei Herzkrankheiten, Ztschr. f. d. ges. Neurol. u. Psychiat. **140**:657-709, 1932. (*b*) Creutzfeldt, H. G.: Ein Beitrag zur Klinik und Histopathologie der Chorea gravidarum, Arch. f. Psychiat. **71**:357-383, 1924. (*c*) Jakob, A.: Die extrapyramidalen Erkrankungen mit besonderer Berücksichtigung der pathologischen Anatomie und Histologie und der Pathophysiologie der Bewegungsstörungen, Berlin, Julius Springer, 1923, pp. 68-87. (*d*) Lewy, F. H.: Die infektiös-toxische Chorea (Chorea minor und gravidarum), in Kraus, F., and Brugsch, T.: Spezielle Pathologie und Therapie innerer Krankheiten, Berlin, Urban & Schwarzenberg, 1924, vol. 10, pp. 751-788. (*e*) Vogt, H.: Chorea minor (Sydenhamsche Chorea, infektiöse Chorea, Veitstanz), in Lewandowsky, M.: Handbuch der Neurologie, Berlin, Julius Springer, 1912, vol. 3, pp. 901-919.

particularly of the frontal lobes; however, little emphasis has been placed on this observation. We have no case of acute uncomplicated articular rheumatism or of acute chorea minor in our series, but several of our patients had had chorea earlier in the course of their disease. In all of these cases we observed healed lesions in the cerebral cortex, but we confess that we were unable to identify with certainty foci in the basal nuclei. This does not imply that foci were not present, and probably the scars still existed.

Pathologists are not agreed as to precisely which of the various lesions is responsible for the motor disorder.[9] In a case of chorea paralytica, or chorea mollis, associated with mitral endocarditis severe degeneration of the muscle fibers was seen, and to this was attributed the transition of the usual picture of chorea to that of chorea mollis.[10]

NEUROPSYCHIATRIC DISORDERS ASSOCIATED WITH RHEUMATIC ENDOCARDITIS

In 21 of the 23 cases of rheumatic endocarditis in this series neuropsychiatric disturbances of one kind or another were recorded. The commonest complication was hemiplegia. This occcurred in 10 instances. Headache had been complained of in 7 cases, but in 2 of these it was presumably not related to the organic disease. Convulsions had occurred in 5 cases, but in 2 of these the relation to the organic disease was questioned. The attacks had been of the grand mal type, but in 1 instance there had also been petit mal seizures. To what extent convulsions in childhood may be related to unsuspected endocarditis remains speculative. Chorea had occurred in 3 cases. There had also been instances of twitching of isolated muscles, athetotic dyskinesias, vertigo, syncope, vomiting, fatigue and general weakness. Aneurysms of cerebral vessels are said to occur in about 2 per cent of cases,[9a] and spontaneous intracerebral hemorrhage, presumably due to rupture of an aneurysm, may be fatal, but even large clots have been removed surgically, with recovery of the patient.[11] In 1 of our cases there had been great diminution in the pupillary reaction to light. Examination of the spinal fluid had been made in 1 case only, and in this it was essentially normal. In this group of cases, as a whole, disturbances in the motor field were striking.

Psychiatric disturbances are common. Usually, they are of short duration and presumably are symptomatic of the infection; however, it is possible that they may lead to more enduring psychoses, as Bruetsch[12] contended. In our series psychoses had occurred in 5 instances, but in 1 the possibility of a relation to

9. (*a*) Brinkmann, F.: Ueber histologische Befunde im Zentralnervensystem bei Endocarditis infectiosa bzw. septica mit cerebralen Störungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **114**:734-750, 1928. (*b*) Toulouse, E.; Marchand, L., and Courtois, A.: Rhumatisme aigu cérébral: Considérations anatomo-pathologiques, Bull. et mém. Soc. méd. d. hôp. de Paris **47**:1119-1121 (June 22) 1931.

10. Marinesco, G.; Draganesco, S.; Axente, S., and Bruckner, I.: Étude anatomo-clinique d'un cas de chorée molle, Ann. de méd. **40**:397-409 (Nov.) 1936.

11. Craig, W. M.: Personal communication to the authors.

12. Bruetsch, W. L.: Psychosen bei chronischer Endokarditis, Psychiat. neurol. Wchnschr. **38**:551 (Oct. 31); 563 (Nov. 7) 1936.

endocarditis could not be established. In 1 case the psychosis had begun abruptly; the patient had had delusions of persecution and had threatened to shoot herself and others. Another patient, who had hallucinations and convulsions for five years, died in status epilepticus. Two had been manic in their behavior. More common, but less severe, reactions included delirium, irritability, increased psychomotor activity, emotional instability, insomnia, depression, neurotic behavior and apathy.

Few pathologic studies have been made of the nervous system of patients who at necropsy were found to have had rheumatic endocarditis. Most of these were in cases in which there was a neurologic complication, such as Sydenham's chorea. Bodechtel [5a] examined the brains of 38 patients; new or old lesions of rheumatic endocarditis were seen. In 9 of the cases changes were observed in the nerve cells; in 6, sizable regions of degeneration were present; in 13 cortical pallor and softening occurred; in 3 inflammatory changes in the sense of "embolic encephalitis" were observed, and in 7 no changes were seen. Thus, there were cerebral lesions in 81 per cent of cases in Bodechtel's series.

Winkelman and Eckel [4] examined the central nervous system in 5 cases in which death had occurred from rheumatic fever. In 4 of these endocarditis was not present, and great proliferation of the endothelial cells of the intima of the smaller vessels of the cortex, some hyaline changes in the walls of other vessels and occasional small regions devoid of cells (*Verödungsherde*) were noted. In the fifth case there were severe vegetative endocarditis and foci of glial proliferation in the nervous system. Bacteriologic studies were not reported; this case may have been one of subacute bacterial endocarditis. The authors concluded that the endothelial proliferation was not specific for rheumatic fever. There was some edema of the brain, an observation on which they laid stress. The endarteritis they attributed to mechanical edema or toxic factors.[13]

It is well known that endocarditis may be attended by extensive vascular disturbances.[14] In 1932 Bell showed that various types of endocarditis gave rise to lesions in the glomeruli of the kidneys; some of these lesions resulted from embolism, but more resulted from thrombosis of the capillaries. Similar vascular occlusions occur in the brain with apparently greater frequency than they do in the kidneys. The damaging effect of such occlusions is more easily demonstrated in the nervous system because of the delicacy of the tissues involved and because nerve cells, once destroyed, do not regenerate.

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13. Winkelman, N. W., and Eckel, J. L.: Productive Endarteritis of the Small Cortical Vessels in Severe Toxaemias, Brain **50**:608-623 (Oct.) 1927.

14. Bell, E. T.: Glomerular Lesions Associated with Endocarditis, Am. J. Path. **8**:639-664 (Nov.) 1932.

In some of the sections that we examined we were certain that the small vessels were occluded by emboli, whereas in others we were equally certain that the vessels were occluded by thrombi formed in situ. When occlusion resulted from embolism, especially when of recent origin, the endothelial cells of the intima were outside the blood clot. In cases of thrombosis in situ, which is probably due to the local effect of cocci or their toxins, the initial lesion was one of swelling of the endothelial cells and a hyalin-like change in the wall (fig. 1). This progressed until the lumen of the vessel was occluded or almost occluded, and the endothelial cells usually could be seen in the middle of the hyalin-like

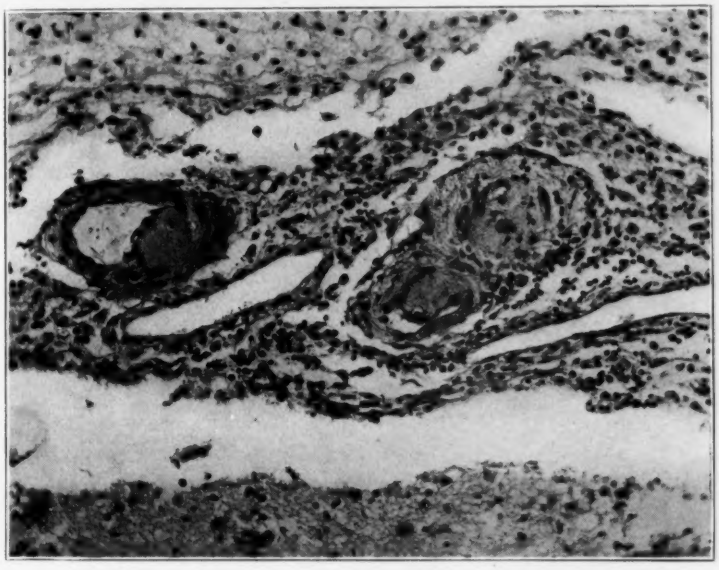

Fig. 1.—Three stages in the occlusion of blood vessels by proliferation of the subintimal connective tissue (from a case of subacute bacterial endocarditis). There is a lymphocytic reaction in the meninges, but organisms were not demonstrable. Cresyl violet; × 135.

thrombus. In some of the large vessels the process was eccentric, and the new lumen, if not completely obliterated, also was eccentric. Mitotic figures might be present (fig. 2). Whether the cause of the vascular occlusion is embolic or thrombotic, the effect on the surrounding nerve tissue seems to be identical.

In order to avoid confusion, we excluded from our study cases in which endocarditis was complicated by senility, injury to the head and tumor of the brain. There were 42 cases of endocarditis available for microscopic study of the central nervous system. In 23 of these the process was of the rheumatic type, chronic and in most instances healed. In several there was evidence of acute or subacute exacerbation of the endocarditis. During any stage of the disease large or small

vegetations may break off and be carried into larger or smaller vessels of the brain, with or without production of transitory or lasting neurologic or psychiatric disturbances.

When emboli lodge in larger vessels infarcts result, which are recognized easily and resemble those of cerebral arteriosclerosis. They may be seen with the naked eye and were observed in 14 of the 23 cases of rheumatic endocarditis. We shall not describe them further.

In several of our cases we observed microscopic lesions at different stages of healing, which were suggestive of successive occlusive lesions or showers of

Fig. 2.—An occluded arteriole (from a case of subacute bacterial endocarditis). It is not certain at this stage whether the occlusion was due to subintimal proliferation or to an embolus. We think it was due to an embolus which was being organized. Note the mitotic figure. Cresyl violet; × 435.

emboli. There were miliary foci from which all nerve cells, and even many of the astrocytes, had disappeared (fig. 3). Foci of this kind were innumerable in the cortex and basal nuclei in 22 of the 23 cases. These foci usually were very small and were at first difficult to recognize unless the Nissl stain or some modification of it was used. They were in reality minute infarcts. There was little reaction in the surrounding tissue.

We were unable to find lesions sufficiently early to observe degenerating nerve cells. With lower powers of magnification these foci appeared as small, pale

regions without cellular reaction (fig. 4). Thus, they were quite different from the Aschoff bodies in the heart. In only 4 cases of the earlier stage of the disease did we note any glial reaction. The nerve cells already had disappeared; the astrocytes were partly degenerated; the oligodendroglia had disappeared, and there were few microglia cells. The outstanding feature of these sections was the absence of nerve cells (fig. 5). The foci varied much in size, and frequently several were fused, which imparted to the cortex an irregular, mottled and distorted appearance, sometimes referred to as "wind blown." We did not see streaks devoid of nerve cells that extended from the pia mater to the white matter, as

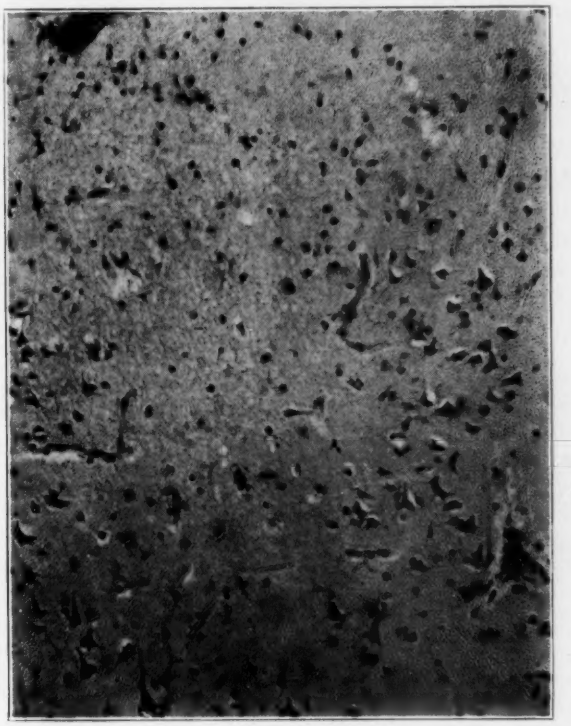

Fig. 3.—A small, recent infarct in the cerebral cortex (from a case of rheumatic endocarditis). Note the edema and absence of nerve cells. Cresyl violet; × 90.

Brinkmann [9a] described. Within the healed foci were chiefly astrocytes (fig. 6); a few microglia cells and occasionally oligodendrocytes were present. Sometimes the surface of the cortex was distorted by the scar.

Frequently, it was possible to find the small occluded blood vessels responsible for these foci. Had we made serial sections of the foci we probably could have found the occluded blood vessels in all foci. The emboli, when seen, were acellular hyalin-like masses. In the older lesions there was, as a rule, no proliferation of the endothelial cells of the blood vessel, no inflammation around the

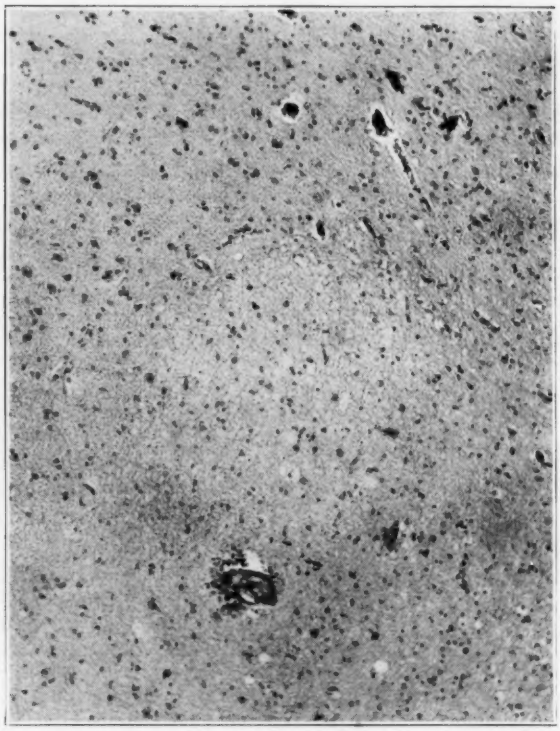

Fig. 4.—A small, recent infarct at the junction of the cerebral cortex and white matter (from a case of chronic rheumatic endocarditis). The edema is better seen here than in figure 3. Cresyl violet; × 75.

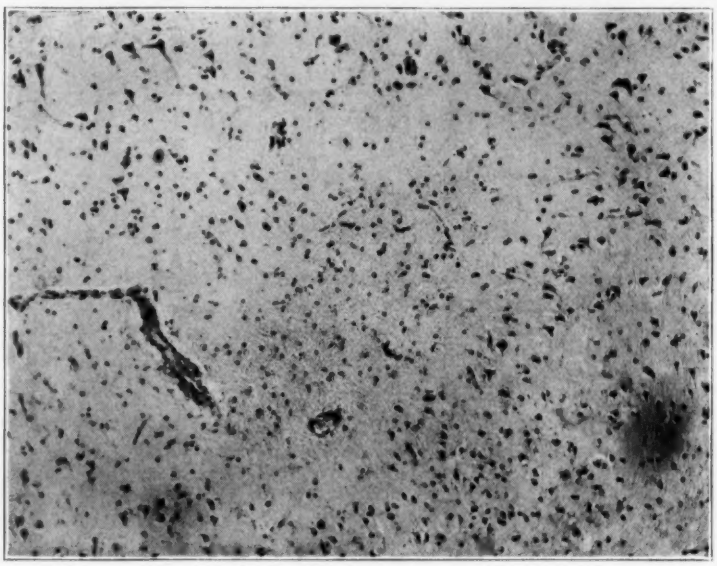

Fig. 5.—An old infarct in the cerebral cortex (from a case of healed rheumatic endocarditis). We have referred to this type of lesion as a glial scar. Note the increased number of glia cells and absence of nerve cells. Cresyl violet; × 80.

vessels and no formation of new vessels, unless the infarct was larger than those which we have been describing. These small acellular foci did not proceed to liquefaction and the formation of cysts (fig. 2).

There was a reaction in the pia-arachnoid in but 1 of these cases. In this case there was a history of rheumatic fever fifteen years previously, and the patient died at the age of 26 years as the result of rupture of a small aneurysm, presumably congenital rather than mycotic, at the junction of the left anterior cerebral and the anterior communicating artery. There was, in addition, a small unruptured aneurysm at the junction of two branches of the left middle cerebral artery. There had been at least one previous rupture of the anterior aneurysm, as indicated by chronic fibrous meningitis with blood pigment around the frontal lobes and the base of the brain. The aneurysm had become adherent to the medial surface of the

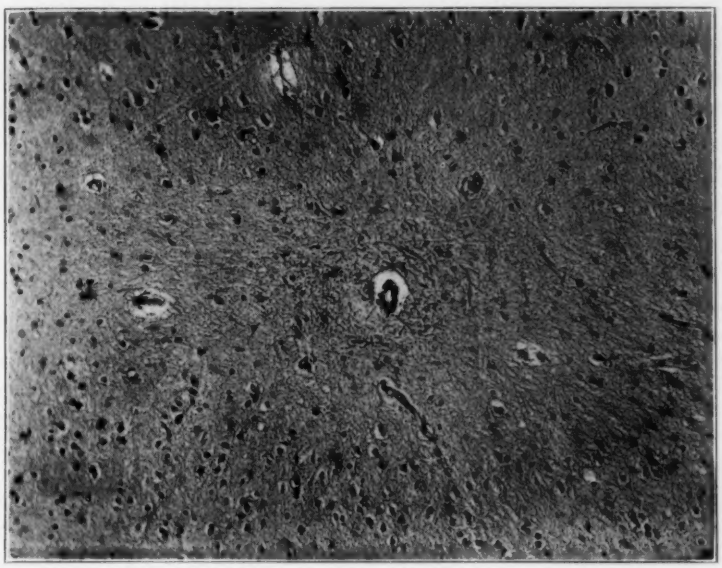

Fig. 6.—Old glial scar (from a case of healed rheumatic endocarditis). The fibrils of astrocytes are visible. Hematoxylin and eosin; × 100.

frontal lobe, and at its final rupture it had bled into the substance of the left frontal lobe and into the anterior horn of the left lateral ventricle.

Although endocarditis was absent in both cases reported by Bender [15] as instances of disseminated alterative arteriolitis, they apparently represented another phase of Libman-Sacks disease, or verrucous endocarditis without bacteremia. In this nonrheumatic, nonbacterial form of verrucous endocarditis there are no Aschoff or Bracht-Wächter

15. Bender, L.: Psychiatric, Neurologic and Neuropathologic Studies in Disseminated Alterative Arteriolitis, Arch. Neurol. & Psychiat. **36**:790-815 (Oct.) 1936.

bodies in the myocardium,[16] but there is diffuse involvement of the endothelium of the capillaries, arterioles and venules of the entire body. In Bender's cases there were headache, lassitude, delirium, hallucinations, disorientation, stupor, retinal hemorrhages, nystagmus, muscular paresis, impairment of tendon reflexes, spasticity, Babinski's sign, pseudoathetosis, ataxia and dysmetria, all of which symptoms and signs indicated diffuse involvement of the brain. An interesting observation made in the first case was that, as the patient expressed it: "Time took too long," a symptom that has been related to decreased rate of blood flow through the brain. Pathologically, there were noted endothelial swelling and proliferation, especially where the arterioles broke into the capillary network; hyalin-like swelling of the walls of vessels, sometimes to the point of obstruction of the lumen; involvement of cortical cells, Purkinje cells and nuclei of the stem, and astrocytic proliferation.

Opinions differ as to whether the lesions in the cerebral blood vessels in cases of rheumatic endocarditis are of embolic or of toxic origin. If they are of toxic origin, they need not be associated with endocarditis. Winkelman and Eckel [13] described proliferation of the endothelial lining of some of the smaller cerebral vessels, a condition which they called productive endarteritis. This differed, however, from that described by Bender, since she made no mention of reactions.

SUBACUTE BACTERIAL ENDOCARDITIS (LENTA)

Much has been written concerning the neurologic findings that are so frequently associated with subacute bacterial endocarditis. The incidence of such involvement is said to be in the vicinity [17] of 20 to 25 per cent, and the incidence of neuropathologic changes much higher.[18] The neurologic disturbances may be sudden or gradual in onset, may dominate the clinical picture completely [19] and may suggest for months such a variety of diagnoses as dementia paralytica,[20] multiple sclerosis and funicular myelosis.[21] The preliminary diagnosis may suggest, among other conditions, Schilder's disease, anterior poliomyelitis, sci-

16. Libman, E.: Characterization of Various Forms of Endocarditis, J. A. M. A. **80**:813-818 (March 24) 1923.

17. Krinsky, C. M., and Merritt, H. H.: Neurologic Manifestations of Subacute Bacterial Endocarditis, New England J. Med. **218**:563-566 (March 31) 1938.

18. De Jong, R. N.: Central Nervous System Complications in Subacute Bacterial Endocarditis, J. Nerv. & Ment. Dis. **85**:397-410 (April) 1937.

19. Diamond, I. B.: Brain Changes in Malignant Endocarditis, Arch. Neurol. & Psychiat. **27**:1175-1208 (May) 1932.

20. Melcher, A.: Ueber Encephalitis bei Endocarditis lenta, Schweiz. Arch. f. Neurol. u. Psychiat. **34**:299-324, 1934.

21. Kimmelstiel, P.: Ueber Viridans-Encephalitis bei Endocarditis lenta, Beitr. z. path. Anat. u. z. allg. Path. **79**:39-68 (Dec.) 1927.

atica, polyneuritis, cerebral hemorrhage, encephalitis lethargica, syphilis and tumor of the brain.[17]

Visual disturbance may include retinitis, optic neuritis, choked disks,[21] blindness of embolic origin[22] or interruption of the tracts. Paralysis of the extraocular muscles, the cervical sympathetic nerves, the face,[20] the palate, the pharynx, the larynx[23] and the tongue may occur.[20] There may be tremor, general and focal convulsions,[20] hemiplegia, ataxia, hemianopia, aphasia[22] and vertigo. Somnolence may be remarkable and has been attributed to mesencephalitis.[24] Meningitis may occur,[25] but it should be pointed out that neutrophilic pleocytosis does not necessarily indicate meningitis, for it may follow softening secondary to embolism or other cause.[26] Although the formation of an abscess is admittedly rare, cases have been described.[27] On the mental side there may be delirium, euphoria and psychoses with schizoid features. Death usually is due not to sepsis but to embolism[28] and to failure of an important organ, such as the brain.

Our group comprised only 9 cases of this type, in 8 of which Streptococcus viridans had been isolated. In 7 of these neuropsychiatric disorders had been conspicuous. Hemiplegia had occurred in 4 cases, hemianesthesia in 2, hemianopia in 1, convulsions in 2, chorea in 1 and hemifacial dyskinesia in 1. Headache, vertigo, tremors, conjugate deviation of the eyes, weakness, fatigue and vomiting also had been observed. In 1 of our cases a history that twenty years previously an illness was associated with diplopia, dysphagia, blepharospasm and muscular weakness pointed to a previous attack of epidemic encephalitis. Clouding of consciousness and irritability had been noted commonly. One child experienced a striking disorder of behavior; he tripped his mother, made sudden attacks on strangers and provoked others with his extreme insolence.

22. Montgomery, L. C.: A Review of the Recent Literature on Subacute Bacterial Endocarditis, Canad. M. A. J. **14**:631-635 (July) 1924.

23. Brulé, M.; Hillemand, P.; Mallarmé, J., and Trelles, O.: Paralysie unilatérale du voile du palais, du pharynx, du larynx, avec syndrome de Claude Bernard-Horner par foyer septique bulbaire au cours d'une endocardite maligne subaiguë, Bull. et mém. Soc. méd. d. hôp. de Paris **50**:1475-1481 (Nov. 16) 1934.

24. Jacarelli, E.: I disturbi del sonno nella lesioni del mesencefalo (contributo anatomo-clinico), Policlinico (sez. med.) **39**:452-466 (Sept.) 1932.

25. Smith, F. J., and Brumfiel, D. M.: Meningitis Complicating Subacute Bacterial Endocarditis, with Report of a Case, Am. Heart J. **2**:446-449 (April) 1927. De Jong.[18]

26. Claude, H., and Oury, P.: Les accidents nerveux de l'endocardite maligne prolongée, Rev. de méd. **39**:449-469 (Aug.-Sept.) 1922.

27. Lemierre, A., and Augier, P.: Endocardite lente à forme psychique, Gaz. d. hôp. **105**:355-357 (March) 1932. Melcher.[20] Rabinowitz, M. A.; Marcus, I. H., and Weinstein, J.: Subacute Bacterial Endocarditis with Large Brain Abscess, J. A. M. A. **98**:806-807 (March 5) 1932.

28. From, M.: Die Todesursachen bei "Sepsis lenta," Schweiz. med. Wchnschr. **65**:698-699 (Aug. 3) 1935. Willius, F. A.: Cardiac Clinics: VI. Clinic on Subacute Bacterial Endocarditis; Sudden Death; Postmortem Findings, Proc. Staff Meet., Mayo Clin. **10**:73-78 (Jan. 30) 1935.

There are numerous studies in the German literature on so-called viridans encephalitis. Kimmelstiel [21] observed lesions in the brain in most of his 11 cases of endocarditis lenta. In 6 of these he recovered Str. viridans from the blood stream, and in 9 he saw organisms in sections of the nervous system. There were several manifestations of infected emboli, such as meningitis, mycotic aneurysms with rupture, abscesses in the brain, embolic encephalitis with inflammation or degeneration and, in 1 case, funicular degeneration of the spinal cord. He reproduced lesions in rabbits with the Str. viridans which he had recovered from 1 of the patients. Nine of 16 rabbits had endocarditis, and 6 had cerebral lesions. Winkelman and Eckel [29] noted changes in the nervous system in all of 8 cases of septic endocarditis, and a small abscess in 1 of 5 cases of subacute bacterial endocarditis. In 2 cases they observed in some of the smaller vessels swelling of the endothelial cells and in other vessels occlusion by hyaline masses. They saw regions from which the nerve cells had disappeared and in which proliferation of the glia cells had occurred but scavenger cells were absent. In 1 case there was a mycotic aneurysm as well. In the fifth case there were regions of necrosis, decrease in the number of nerve cells and perivascular phagocytosis. Melcher [20] studied 10 cases of endocarditis lenta, in 7 of which the clinical diagnosis of encephalitis endocarditis lenta had been made.

Numerous other studies of the nervous system have been made in cases in which death occurred from subacute bacterial endocarditis, such as those of Nathan,[30] Zolotowa,[31] Brinkmann [9a] and De Jong.[18] The changes may be summarized as follows: (1) *Verödungsherde*, or acellular regions; (2) *Erweichungsherde*, or glial foci; (3) small or large abscesses; (4) mycotic aneurysms, and (5) meningitis.

In every case of subacute bacterial endocarditis in which we performed an examination we observed in the central nervous system widespread reactions based on occluded arterioles or capillaries. There were small foci that were almost pathognomonic of the disease, although Spielmeyer [32] noted similar lesions in cases of typhus fever. Proliferation of vascular endothelial cells distal to the site of the embolus sometimes occurred. Usually there were few newly formed vessels. The focal reaction around the occluded vessels was characteristic. Nerve cells in and at the edge of the cortical foci or basal ganglia were degenerated,

29. Winkelman, N. W., and Eckel, J. L.: The Brain in Bacterial Endocarditis, Arch. Neurol. & Psychiat. **23**:1161-1182 (June) 1930.

30. Nathan, H.: Ueber Viridans-Encephalitis, Ztschr. f. d. ges. Neurol. u. Psychiat. **126**:536-544, 1930.

31. Zolotowa, N. A.: Gehirnveränderungen bei Endokarditis, Virchows Arch. f. path. Anat. **277**:420-430 (May 12) 1930.

32. Spielmeyer, W.: Infektion und Nervensystem, Ztschr. f. d. ges. Neurol. u. Psychiat. **123**:161-203, 1930.

but nerve cells close to, and at times even in, the zone of the glial reaction were normal (fig. 7 *A* and *B*). In the white matter of the brain or spinal cord the myelin sheaths and axis-cylinders involved in the glial scars were degenerated.

The astrocytes (fig. 8) were marked by proliferation. They had lost, for the most part, their attachments to the walls of the blood vessels and were collected around the vessels in an irregular manner. There were few swollen or fused (gemästete) glia cells. Mitotic figures were rare. Oligodendroglia cells had disappeared. Microglia cells frequently occurred in such numbers as to justify the term *Stäbchenzellenencephalitis* (fig. 9). Polymorphonuclear leukocytes or lymphocytes were not present. These foci simulated the Aschoff bodies of the myocardium, except that there were few multinucleated cells and the reaction was purely ectodermal.

Not all foci were like those already described. In their earliest forms, portions usually were almost completely devoid of cells, as in the cases of rheumatic fever, but in addition there was edema. Later the astrocytes proliferate and their vascular attachments are broken, but as yet fibrous astrocytes or glia fibrils were not present and distortion of the surrounding tissue had not occurred. For this early stage we prefer the term "glial foci" to that of "glial scars." We did not note abscesses in this series of cases; the reaction was one of macroglial and microglial proliferation. The foci occurred in all parts of the brain and spinal cord and had no predilection for any particular layer of the cortex. When these glial foci lay beneath the ependymal lining of the ventricles, some of the overlying ependymal cells disappeared, and at the edges slight proliferation occurred. In the meninges of most of the specimens we noted many localized regions of reaction with histiocytes, some lymphocytes and young connective tissue cells; but in none was there generalized meningitis. We did not see foci in the choroid plexus, mycotic aneurysms or hemorrhages in the brain or meninges.

ACUTE INFECTIVE BACTERIAL (SEPTIC) ENDOCARDITIS

In acute infective endocarditis, also, gross involvement of the brain is common.[19] However, it is often accompanied by sepsis of both the brain and the meninges. Embolism, meningitis, abscess and their concomitant clinical pictures appear. Aneurysms are said to occur in 9 per cent of cases,[9a] and may lead to hemorrhages.[5] Chorea has also been noted,[32a] as have various parakinesias, such as scratching, parkinsonism and choked disks.[29] Psychiatric disturbances may dominate the picture.

Acute infective endocarditis was represented in 10 cases of our series, and in all of these neurologic or psychiatric disturbances had been present. Irritative motor disturbances, such as muscular twitching, tremor, convulsions, chorea, hiccup and dyskinesias, had occurred in 5 cases. The dyskinesias were expressed as a persistent chewing movement, rhythmic protusion of the tongue and myoclonus of the extremities. Inequality and immobility of the pupils, dysarthria, insomnia, somnolence, vertigo, nausea and pathologic plantar responses had been noted. In 3 cases hemiplegia had occurred. In 2 cases the picture had been frankly that of encephalitis, and in 2, that of meningitis. In 1 case a diagnosis of acrodynia

32a. Shaw, D.: A Confusional State Associated with Infective Endocarditis, J. Ment. Sc. **81**:435-437 (April) 1935; Brit. M. J. **1**:1313-1314 (June 29) 1935.

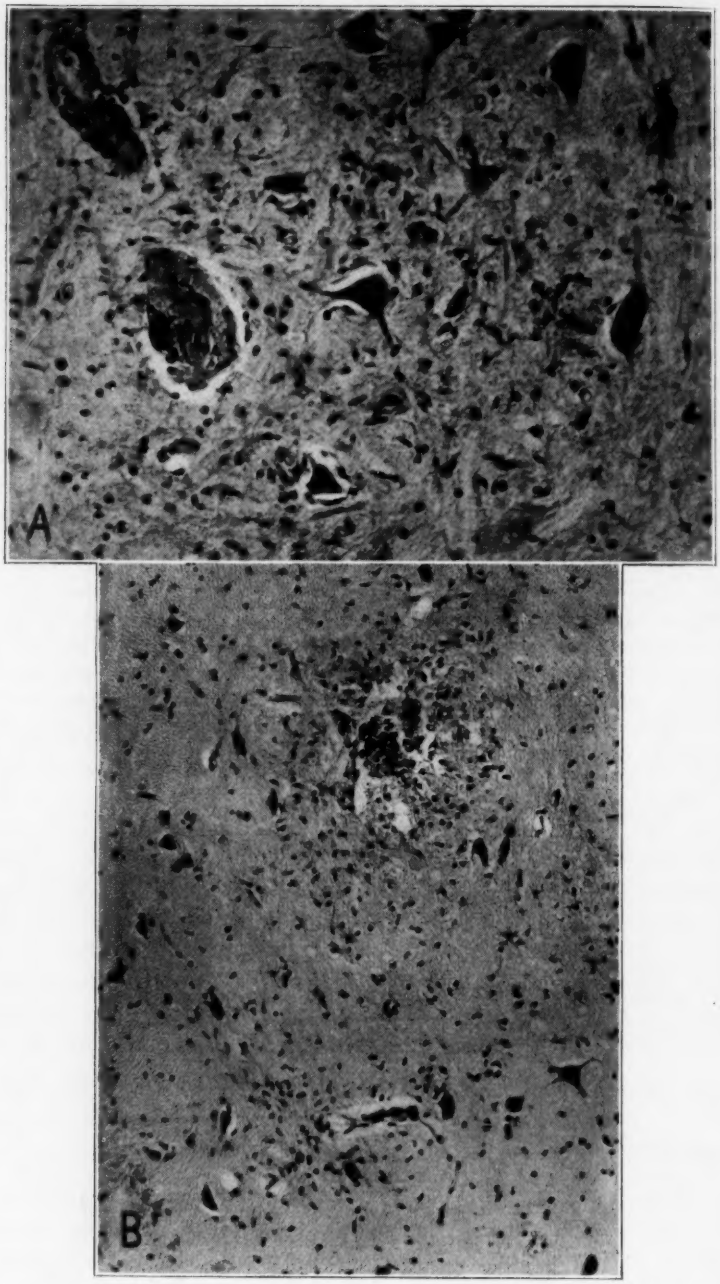

Fig. 7.—*A* (× 190), a recent glial focus, the result of an embolus in the small arteriole at the left (from a case of subacute bacterial endocarditis). Note the glial reaction surrounding a well preserved nerve cell. *B* (× 165), a small, recent glial focus which is comparatively sharply circumscribed (from a case of subacute bacterial endocarditis). Note also the microgliosis around the capillary at the bottom of the field. Cresyl violet.

Fig. 8.—A perivascular glial focus with some edema (from a case of subacute bacterial endocarditis). Note the sharp outline. Hematoxylin and eosin; × 165.

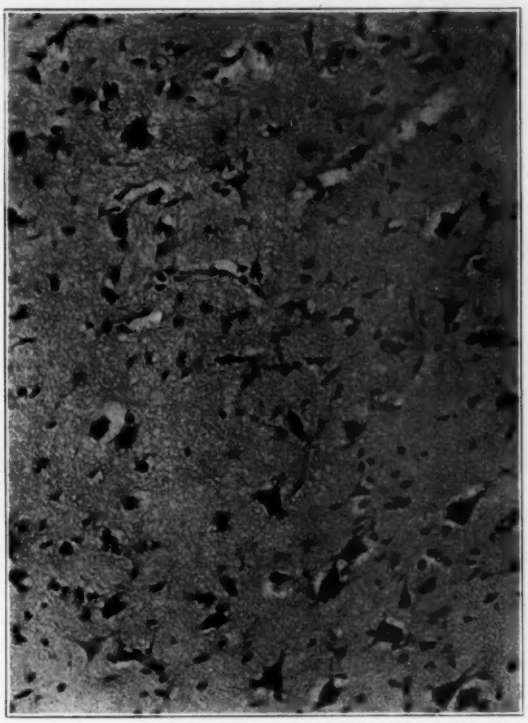

Fig. 9.—Diffuse cortical microgliosis, *Stäbchenzellenencephalitis* (from a case of subacute bacterial endocarditis). Cresyl violet; × 200.

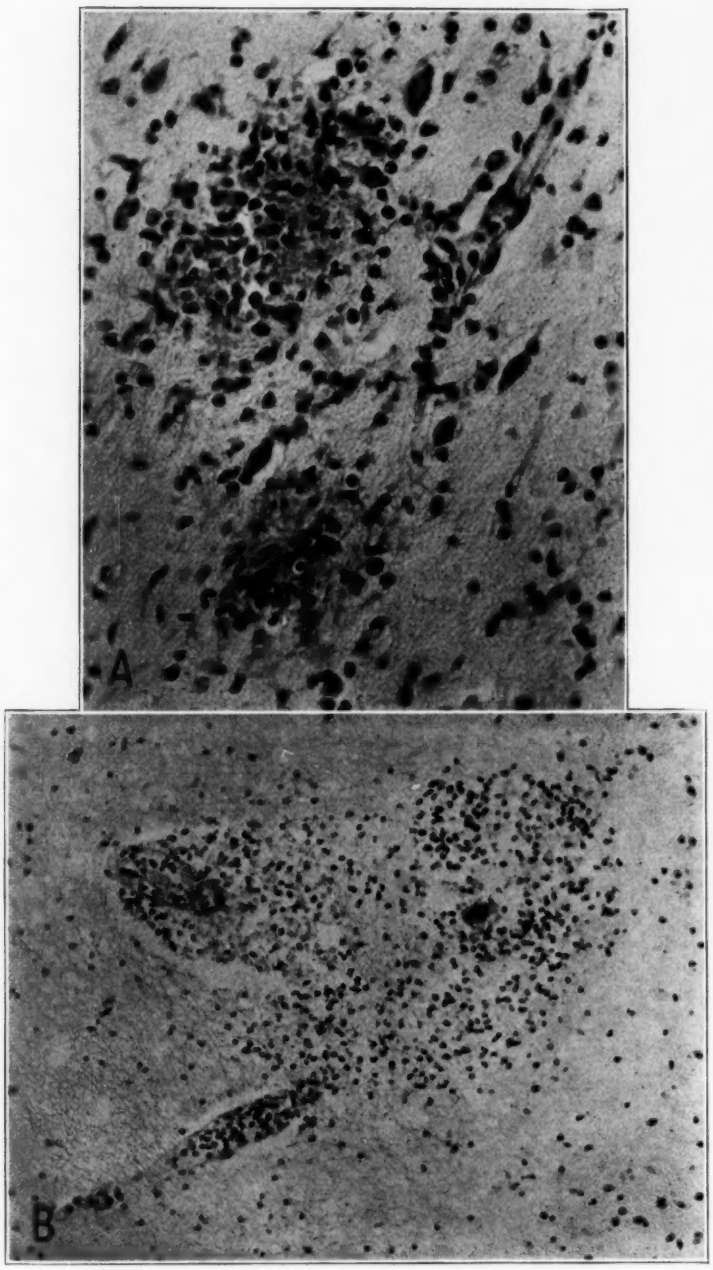

Fig. 10.—*A* (× 280), two acute foci of gliosis, with some necrosis and lymphocytes (from a case of subacute bacterial endocarditis). There are some pyknotic degenerating glia cells. *B* (× 145), a focus in the brain (from a case of septic endocarditis). A colony of bacteria is surrounded by a region of necrosis that contains polymorphonuclear leukocytes. Two small vessels are dilated, and their lumens are occluded by septic thrombi. Cresyl violet.

also had been made. Spinal punctures had been made in 3 instances. In 1 case the results were within normal limits, and in 2 there was a predominantly neutrophilic pleocytosis.

On the mental side, there had been observed particularly clouding of consciousness, increased psychomotor activity, emotional instability, faulty attention and limited orientation, delirium, irritability and, less often, apathy.

Of the 10 cases of acute bacterial endocarditis, we recovered hemolytic streptococci from the blood in 4, pneumococci in 2, staphylococci in 1 and meningococci in 1, and Proteus ammoniae from the brain and valves of the heart in 1. In 1

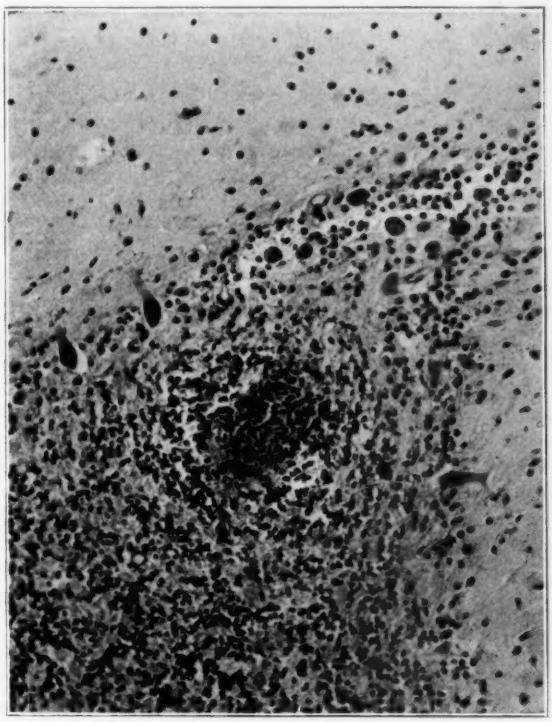

Fig. 11.—Small, recent glial focus in the granular layer of the cerebellum (from a case of subacute bacterial endocarditis). Cresyl violet; × 145.

case, in which the specimen had been sent from elsewhere to the laboratory for study, bacteriologic examination was not carried out.

Multiple abscesses were observed in the central nervous system in all but 1 case, in which the organism isolated was the meningococcus. In this case the histologic picture approached that of Str. viridans in that there were small glial foci and minute acellular regions in the superficial layers of the cortex. There were also chronic, but almost healed, meningitis and ependymitis. The brains in the 9 other cases contained many abscesses of various sizes. Within the younger and smaller abscesses we could almost always see a small vessel occluded by an infected thrombus and around it an edematous region comparatively free of cells.

Later, polymorphonuclear leukocytes appeared in the perivascular space (fig. 10 *A*), and still later they occupied the entire focus, spreading even into the surrounding brain (fig. 10 *B*).

In older abscesses the occluded vessel was rarely seen. Frequently, dense colonies of organisms were present in the center of the lesion. The abscesses varied in size and sometimes two or more became fused. We observed several abscesses in which hemorrhages had occurred. The abscesses were similar in cellular structure, irrespective of the type of invading organism, and the surrounding brain reacted to all in the same way. Surrounding the cortical abscess was a zone of edema in which the nerve cells had degenerated, the astrocytes had undergone clasmatodendrosis and all oligodendroglia cells had disappeared. Proliferation and immigration of microglia cells were limited, and we saw none being transformed into scavenger cells.

In 1 case both Streptococcus haemolyticus and Str. viridans had been recovered from the blood stream, and in another a bacteriologic examination had not been made. In both these cases the histologic changes differed from those in the other cases in that the reaction around occluded vessels indicated a varying combination of glial proliferation and leukocytic reaction. Most foci contained proliferated astrocytes, polymorphonuclear leukocytes, occasional lymphocytes and, usually, many microglia cells in the form of rod cells. The centers of these foci frequently contained nuclear debris, around which were polymorphonuclear leukocytes; surrounding these, in turn, were lymphocytes; at the edge were astrocytes with hyperchromic nuclei. In the surrounding brain there frequently were many microglia (rod) cells, their long axes pointing toward the foci. We did not note any colonies of organisms in these small discrete abscesses. In these 2 cases foci were present in every part of the central nervous system, including the granular layer of the cerebellum (fig. 11) and the spinal cord. Frequently, as many as six small, discrete abscesses were visible in one microscopic field under low power, but fusions, such as occurred in cases of the more septic types, were not present. Near the superficially placed foci were also many regions of localized meningitis, in which there were histiocytes, fibroblasts, many lymphocytes and, frequently, polymorphonuclear leukocytes. In 4 of the other 8 cases there was diffuse purulent meningitis. We did not observe aneurysms in any of them.

COMMENT

Necropsy was performed in each case of this series; thus, sweeping inferences cannot be drawn regarding the group in which the termination was not fatal. This is especially true of the clinical aspects of these cases. Both neurologic and neuropathologic changes are of frequent occurrence in the presence of endocarditis. We directed our efforts toward correlating more closely, if possible, the neurologic manifestations with the various types of endocarditis.[33] With all types there may occur headache, vertigo, hemiplegia, convulsions, dyskinesias, irritability and delirium. The fact that the course of rheumatic endocarditis may be protracted alters the complete picture in such a manner

33. Flater, A.: Endokarditis und Gehirn, Klin. Wchnschr. **3**:2094-2096 (Nov. 11) 1924.

that one may become lost among the signposts and may not readily see the picture as a whole. With subacute bacterial endocarditis the neurologic and psychiatric symptomatology is often rich and prominent. Indeed, this may so color the picture that the total situation may escape the observer for weeks. With bacterial endocarditis there, too, is a wide range of neurologic and psychiatric complications, but the events are compressed and tied together by the picture of sepsis. Doubtless all the neurologic and psychiatric complications of endocarditis are influenced not only by the underlying disease but by the factor of time, and it may not be possible to go beyond these rather broad generalizations. It must be admitted that this series was not sufficiently large to do this better than it already had been done in part by other investigators.

For a long time psychoses have been known to occur with cardiac diseases even when endocarditis is not present. In all likelihood, they are only in part dependent on the cardiac or circulatory condition.[32] They appear to occur more frequently in older persons, are often sudden in onset and generally carry a good prognosis for recovery even though the prognosis, so far as the heart is concerned, is not necessarily good; these psychoses, however, tend to recur. Disorientation is a common feature. That toxic psychoses may result from poisoning with digitalis is well known, and it is not unlikely that cerebral lesions will be found associated with this condition. In our cases digitalis appeared to play no part, although it had been administered frequently, particularly to patients who had rheumatic endocarditis.

Bruetsch [12] suggested that cerebral damage incidental to chronic endocarditis may be an important, but as yet not generally appreciated, factor in the production of chronic major psychoses. His opinion was based in part on the following arguments: Endocarditis occurred in 8.1 per cent of patients who had endogenous psychoses, such as schizophrenia, paranoia, manic-depressive psychoses and involutional psychoses. Endocarditis occurred in only 1 per cent of cases of dementia paralytica, the cause of which is already conceded to be due to organic disease of the brain. The relationship of endogenous psychoses to endocarditis is more than casual. Voppel [34] also demonstrated at necropsy pericarditis or endocarditis in 9.3 per cent of 171 cases encountered in an institution. It is well known that the cardiac lesions cannot always be detected on clinical examination. Perhaps this can be done in 50 per cent of cases. However, the history of rheumatism is, of course, strongly suggestive of the presence of cardiac lesions.

Bruetsch [12] also called attention to the frequency of old infarctions of other organs, such as the spleen, in cases in which psychoses had also

34. Voppel, cited by Bruetsch.[12]

been of long standing. In these cases, as indeed was often demonstrated, the brain may have been damaged by infarction, as the other organs had been. The early history of these patients, had it been available, might well have revealed a psychosis in keeping with an exogenous cause, which was later followed by reactions classifiable under the more usual syndromes occurring among inmates in state hospitals. That some of these patients look physically ill at the inception of the disease is beyond question. How important an organic substratum may be in the development of a psychosis and how nicely it fits into the resultant picture becomes apparent when the cogent arguments advanced by Singer [35] are thoughtfully considered.

Finally, Bruetsch [12] cited 2 cases of inadequately treated dementia paralytica in which the duration of the disease had been twelve and fifteen years, respectively. Something obviously had prevented the earlier death of these patients. Bruetsch offered the explanation that the rheumatic infection had altered the reticuloendothelial system, much as malaria does, and thus had led to a more protracted course of the disease. Thus, the infection responsible for the endocarditis had an effect the reverse of causing a psychosis; it prolonged a psychosis that usually has a much shorter duration. In almost all the cases cited he was able to demonstrate with the aid of supravital neutral red that the endothelial cells of the blood vessels were diseased.

That a psychosis may be intimately related to endocarditis and to the ensuing cerebral damage will be granted readily, even if such a psychosis cannot be recognized solely by its clinical features. After all, the pattern of a psychosis is determined in a large measure by the possible reactions of the personality. Some of our cases were obtained from the Rochester State Hospital, and in several of these the rheumatic endocarditis clearly antedated the onset of the mental disturbances. The presence of many foci of destruction in the brain, as Bruetsch and Bodechtel contended, is at least suggestive of a possible relationship between endocarditis and mental disease, such as exists between endocarditis and the less debatable neurologic complications. We have not considered the cardiac lesions or the complications in other organs, such as the kidneys, since this has been admirably done by Bell [14] and others. Lesions can be seen in the nervous system in a much higher percentage of cases than in the kidneys. In 25 (96 per cent) of 26 cases of rheumatic endocarditis and in all forms of bacterial endocarditis, we observed cerebral lesions. We devoted most of our attention to the cerebral cortex because it is easier to find lesions there than in the basal nuclei. In the latter, however, it was easy to see the lesions that

35. Singer, H. D.: Psychosis and Central Autonomic Nervous System, J. A. M. A. **110**:2048-2053 (June 18) 1938.

occurred in association with subacute and acute bacterial endocarditis, but it was difficult to identify with certainty the small foci associated with rheumatic endocarditis.

SUMMARY

The sequence of pathologic and clinical events in many of the neurologic complications associated with endocarditis, such as hemiplegia, jacksonian attacks, hemianopia, aphasia, cerebral hemorrhage, abscess of the brain and meningitis, is comparatively clear. That neurologic disorders less prominent than those mentioned may be associated with endocarditis will hardly be questioned. The relationship between pathologic lesions in the brain and psychiatric disorders symptomatic of them will be granted. That some of the major functional psychoses may be related to endocarditis is controversial.

Pathologic studies of the central nervous system have disclosed beyond question that changes in the central nervous system, with or without associated clinical symptoms, are not only common to all types of endocarditis but also are as distinctive as are the various types of endocarditis and that they may be correlated one with the other. It must be clear that more careful neurologic and psychiatric surveys of patients who have endocarditis would augment information and probably would indicate a greater incidence of such symptoms than is now appreciated.

SUBDURAL SHADOWS IN PNEUMOENCEPHALOGRAMS

THEIR DIAGNOSIS, ORIGIN AND SIGNIFICANCE

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The presence of gas in the subdural space is not infrequently observed after and during lumbar pneumoencephalography.[1] It has been proved at operation and at autopsy that the gas actually lies within the subdural space.[2] The resultant subdural shadows have often been a source of confusion to the diagnostician, and are frequently interpreted as "gross cerebral atrophy." Recently, the presence of subdural shadows in encephalograms has been considered indicative, if not diagnostic, of subdural hematomas.[3] Introduction of air into the subdural space has been recommended in the treatment of post-traumatic headache.[4]

There has been some difference of opinion concerning the mode of entry of gas into the intracranial subdural space after its presumptive introduction into the vertebral subarachnoid space. It is apparent that the mode of entry has a direct bearing on the diagnostic and therapeutic value of subdural gas.

It is the purpose of this communication to outline the means by which subdural gas may be recognized, to present certain evidence

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From the Neurological Unit of the Boston City Hospital and the Department of Neurology of Harvard Medical School.

1. Lemere, F., and Barnacle, C. H.: Encephalography: A Review of Eight Hundred Encephalograms with Special Reference to Subdural Air, Arch. Neurol. & Psychiat. **35**:990 (May) 1936.

2. Cramer, F.: A Note on the Occurrence and Significance of Air in the Subdural Space After Encephalography, Bull. Neurol. Inst. New York **3**:506 (March) 1934. Lemere and Barnacle.[1]

3. Holt, W. L., Jr., and Pearson, G. B.: Chronic Bilateral Subdural Hematoma: Encephalographic Diagnosis with Report of Three Cases, Arch. Neurol. & Psychiat. **37**:1161 (May) 1937.

4. Penfield, W., and Norcross, N. C.: Subdural Traction and Post-Traumatic Headache, Arch. Neurol. & Psychiat. **36**:75 (July) 1936.

concerning its mode of entry into the subdural space and to discuss its clinical significance.

ANATOMIC RELATIONS (FIGS. 1 AND 2)

The subdural space in man is a potential space between the arachnoid and the dura.[5] Penfield [6] has presented evidence that a capillary layer of fluid occupies this space during life. The subdural space is continuous

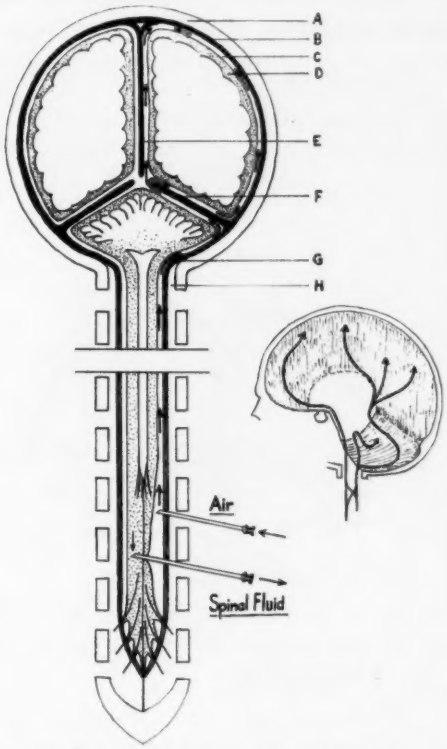

Fig. 1.—Diagram showing lumbar subdural injection of air. *A* indicates bone; *B*, the dura; *C*, the subdural space (distended); *D*, the subarachnoid space; *E*, the falx; *F*, the tentorium; *G*, the point of attachment of the spinal dura to the bone at the foramen magnum, and *H* the spinal epidural space.

In order to demonstrate and emphasize the continuity of the subdural space around the incisura tentorii, continuity of the dura and the subarachnoid space has been broken at the junction of the falx and the tentorium.

The route taken by the air is shown by ascending arrows; that by the spinal fluid, by descending arrows.

The various routes to the hemispheres are shown in the lateral view.

5. Weed, L. H.: Studies on Cerebro-Spinal Fluid: III. The Pathways of Escape from the Subarachnoid Spaces with Particular Reference to the Arachnoid Villi, J. M. Research **26**:51 (Sept.) 1914.

6. Penfield, W.: The Cranial Subdural Space, Anat. Rec. **28**:173, 1924.

from vertex to cauda, without such adhesions as normally exist between the dura and the bone at the foramen magnum.[7] It is potentially present at all places where arachnoid and dura are in apposition. Transition from the subtentorial to the supratentorial subdural space occurs around the dural edge at the incisura tentorii.

Arteries and veins sheathed with arachnoid pass through the subdural space in transit to and from the central nervous system and the dural sinuses. As will be seen later, these vessels constitute weak points at which the arachnoid may be torn.

DIAGNOSIS (FIGS. 3 AND 4)

Because the presence of subdural gas after encephalographic examination is apparently unappreciated in many otherwise well

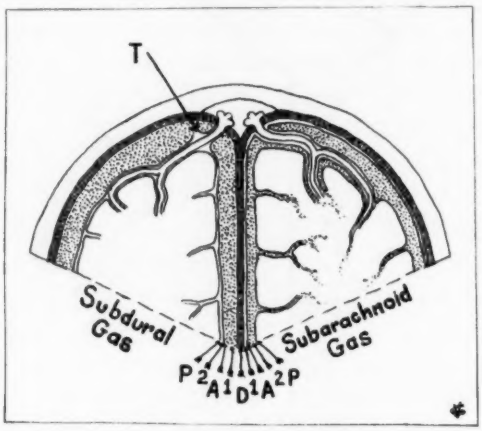

Fig. 2.—Drawing showing hemispheric subdural and subarachnoid spaces distended with gas. *D*, indicates the dura; *1*, the subdural space; *A*, the arachnoid; *2*, the subarachnoid space; *P*, the pia, and *T*, the ruptured arachnoid along a stretched vein.

informed circles, a few words as to its identification are advisable. Intravertebral subdural gas shadows have not yet been differentiated from subarachnoid shadows. On the other hand, intracranial subdural gas has been accurately located above and below the tentorium.[8] The primary characteristic of gas shadows in the subdural space is that they have smooth upper and lower borders, whereas subarachnoid shadows present irregular convoluted lower borders. Gas in the subdural space presses the arachnoid against the cerebral or cerebellar

7. Stone, R. S., and Jones, O. W., Jr.: Encephalography, Radiology **21**:411 (Nov.) 1933.

8. Davidoff, L., and Dyke, C.: The Normal Encephalogram, Philadelphia, Lea & Febiger, 1937.

tissue, obstructing the sulci and thus preventing the gas from outlining the convolutions. The result is a smooth or wavy border over the cerebral or cerebellar hemispheres.

Unless encysted by adhesions or masses, gas within the subdural space is freely mobile and hence will collect in the uppermost parts of the subdural space. Accordingly, subdural shadows vary greatly in location and appearance, according to the position of the head when the roentgenogram is taken.

Subtentorial subdural air occurred alone in 20 per cent of this series of cases and in combination with supratentorial subdural air in 37

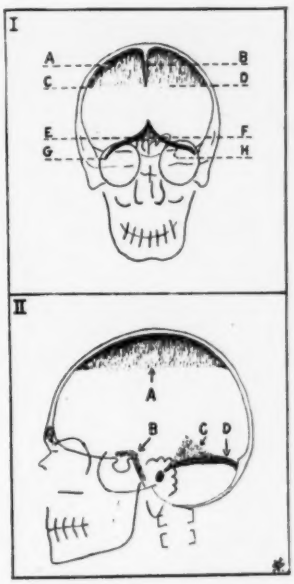

Fig. 3.—Subdural air shadows. I is an anteroposterior exposure with the head erect, showing: hemispheric cap with the smooth wavy lower border of the uppermost band *(A)*, the falx *(B)*, the meniscus at the lower lateral edge *(C)* and the indistinct lowermost border *(D)*; the subtentorial angle with the smooth upper border of band beneath the tentorium *(E)*, the pyramid at the apex of the tentorium *(F)*, the edge of the lateral sinus *(G)* and the smooth lower border over the cerebellum *(H)*.

II is a lateral exposure with head erect, showing: the same hemispheric cap *(A)* shown in I, the suprasellar and supraclival basilar shadow *(B)*, the subtentorial angle *(C)* and the band along the lateral sinus *(D)*.

In order to avoid confusion the subdural shadows are drawn darker than would be seen in the roentgenogram, and ventricular and subarachnoid shadows are omitted, although they usually accompany the subdural shadows.

per cent. When roentgenograms are taken with the patient sitting up, these subtentorial shadows form an inverted V in the anteroposterior or the posteroanterior exposures. In the lateral exposures they form a

triangle. Such shadows are almost invariably bilateral and are frequently mistaken for cerebellar atrophy. Their sole value lies in outlining any distortion of the tentorium.

Subdural shadows over the hemispheres are more frequent, and even more confusing to the diagnostician. In anteroposterior and posteroanterior views taken with the head erect, they are broad, unilateral or bilateral shadows at the vertex, presenting a smooth wavy lower border. In addition, there is a faint shadow forming a cap over the hemisphere. This usually presents a slightly curved lower border, owing to the curvature of the skull cap. In lateral views the same faint cap is seen

Fig. 4.—Roentgenograms showing intracranial subdural air introduced by way of the lumbar subdural space. For nomenclature, see figure 3.

with a faint lower border, a smooth or wavy hemispheric outline and a broad band above the hemispheres. Subdural shadows are often seen along the falx in conjunction with subdural hemispheric shadows.

In roentgenograms taken when the patient is in a recumbent position, the characteristics of the subdural shadows vary with the position of the head. Thus, in anteroposterior brow-up and posteroanterior face-down views the cap of gas is indistinct, creating merely a diffuse increase of shadow in the frontal and occipital fossas, respectively. In lateral recumbent views there is a diffuse shadow over the central temporoparietal area. Lateral brow-up views, however, show a distinct cap of

subdural gas in the frontal fossa (fig. 5). This has been mistaken for localized atrophy of the frontal lobe.[9] A similar cap appears in lateral face-down exposures over the occipital poles. Subtentorial subdural air in the face-down view appears in either the posteroanterior or the lateral exposure as a triangular shadow just beneath the torcular Herophili.

Occasionally, basilar subdural gas appears above and posterior to the sella turcica. Such gas fails to rise into the basilar cisterns and presents flat, horizontal upper and lower borders (figs. 3 and 4). The appearance of such basilar shadows indicates that the gas has been introduced by way of the lumbar subdural space. This constitutes a technical error and is hence of no diagnostic significance. The conformation of the shadows may, of course, be of some value.

Fig. 5.—Subdural air in the frontal fossa as seen in a lateral exposure taken in the recumbent, brow-up position.

Not infrequently a combination of subarachnoid and subdural shadows in the same roentgenogram renders identification of the subdural component difficult. Most erroneous diagnoses are made under these conditions. It is essential to acquire familiarity with this combination (fig. 6). Subdural air over a hemisphere may allow the brain to fall away, thus depressing the homolateral ventricle and even shifting it slightly to the opposite side. Such a situation is often confused with the similar picture produced by a true mass, such as a subdural hematoma.[10]

9. See Bumke's illustration of Pick's disease (Bumke, O.: Lehrbuch der Geisteskrankheiten, ed. 3, Munich, J. F. Bergmann, 1929, p. 592, fig. 84).

10. von Storch, T. J. C., and Munro, D.: Encephalography in the Diagnosis of Subdural Hematomas, New England J. Med. **218**:6 (Jan. 6) 1938.

MODE OF ENTRY

There are three probable ways by which a gas might gain entry to the intracranial subdural space during or after lumbar encephalographic examination. 1. It might be introduced into the lumbar subdural space during the procedure, either directly from the puncture needle or into the subarachnoid and back into the subdural space through tears in the arachnoid. From the lumbar subdural space it could ascend with ease to the intracranial space (fig. 1). 2. Gas might enter the intracranial subdural space directly through tears in the intracranial arachnoid after its introduction into the subarachnoid space in the usual manner.

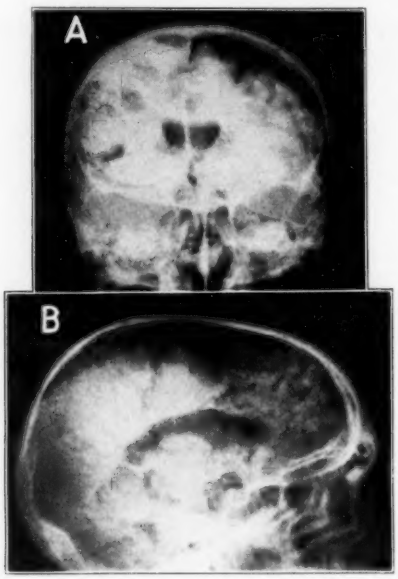

Fig. 6.—Combined subdural and subarachnoid air.

In the anteroposterior view *(A)* note the generalized cortical atrophy, the subarachnoid shadows over the hemisphere on the viewer's left, the subarachnoid and subdural shadows on the opposite side, the subarachnoid cerebellar shadows and the slight depression and shift of the ventricles, due to the subdural air.

In the lateral view *(B)* note the combination of subarachnoid and subdural air over the hemispheres and the subarachnoid basilar and cerebellar air. Compare with figure 4.

This transfer might occur during or after the encephalographic procedure. 3. It is possible that during or after the examination gas might pass through the intact arachnoid from the intracranial subarachnoid to the subdural space.

1. It has been shown in the cadaver that a gas may be injected into the intracranial subdural space by way of the lumbar intravertebral subdural space.[7] It seems mechanically improbable that a lumbar puncture needle could be inserted

into a patient so that its point punctured the dura and yet failed to puncture the arachnoid. However, certain observations have indicated that such a situation may occur. The method of performing encephalographic examination in this clinic entails double lumbar puncture while the patient is in a sitting position.[11] On several occasions the first puncture was successful whereas the second needle apparently did not enter the subarachnoid space. Cerebrospinal fluid flowed readily from the first needle, but no fluid could be obtained from the second. At the same time air could be easily introduced into the second needle.

Under such conditions the point of the second needle might lie within the subarachnoid space, its tip covered by a valvelike piece of tissue. If so, air introduced through it would be found in the roentgenograms to lie, at least partially, in the intracranial subarachnoid space. The point of the needle might lie in loose areolar tissue in the epidural space. In this case only a small amount of air could be injected, none of which would enter the cranium at the foramen magnum.[12] If the needle was outside the vertebra it is apparent that gas could not be introduced through it into the cranium. On the other hand, if the point of the needle lay within the subdural space it would be expected that all of the air introduced through it would ultimately be demonstrable in the intracranial subdural space.

In order to determine whether it was possible to introduce air into the intracranial subdural space in this fashion, the cerebrospinal fluid was drained from the first needle while air was simultaneously introduced into the second according to the usual technic.[11] The roentgenograms taken immediately after replacement (without altering the patient's position) demonstrated that all of the air lay within the intracranial subdural space (fig. 4). The same procedure in several other cases yielded identical results.

In all of these roentgenograms air was demonstrated in the basilar subdural space. It is never seen in this situation under any other condition. This is additional evidence that the air was actually introduced into the lumbar subdural space, from whence it ascended to the intracranial basilar, subtentorial and hemispheric subdural spaces. This confirms the opinions of Pendergrass [13] and Stone and Jones.[7]

It is hardly worthy of consideration that all of the air might have been introduced into the lumbar subarachnoid space, from whence all of it passed through tears in the spinal arachnoid back into the subdural space. If such were the case, cerebrospinal fluid should have been readily obtainable from the needle. Furthermore, it is inconceivable that all of the air should have escaped from the subarachnoid to the subdural space without leaving a tract of gas in the ventricles or subarachnoid spaces. The same line of reasoning makes it appear improbable that the air might have entered the subdural from the subarachnoid space at the base of the skull.

Therefore, it may be concluded that during lumbar encephalographic examination gas may gain entry to the intracranial subdural space by direct introduction into the lumbar subdural space.

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11. von Storch, T. J. C.: On the Technique of Encephalography, with Special Reference to the Use of Apparatus, Am. J. Roentgenol. **35**:78 (Jan. 6) 1936.

12. Unpublished experiments by one of us (V. S.).

13. Pendergrass, E. P.: Encephalography: An Explanation of a Possible Error in Technique, Am. J. Roentgenol. **25**:754 (June) 1931.

2. It is likely that air introduced into the intracranial subarachnoid space may pass into the subdural space through tears in the arachnoid. Not infrequently, roentgenograms taken several days after the encephalographic procedure show collections of subdural air that had not previously been present. Tears occurring before or during the procedure would be expected to cause visible collections of subdural air in the first encephalogram. Tears subsequent to the examination would result in subdural air only at a later date.

It has been demonstrated several times in this clinic that subarachnoid air can pass from the subarachnoid into the subdural space after the encephalographic procedure. In 1 such case the encephalogram taken immediately after replacement of cerebrospinal fluid showed adequate filling of the ventricles and subarachnoid space without evidence of air in the subdural space (fig. 7). Twenty-four hours later roentgenograms demonstrated that almost all of the subarachnoid air had passed into the subdural space (fig. 7). Similar observations have been made in many other cases in this and other clinics.

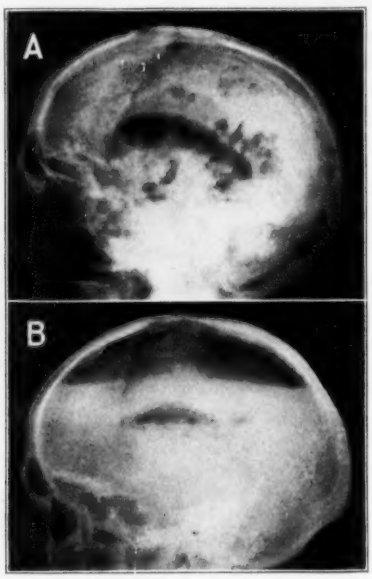

Fig. 7.—Subdural air twenty-four hours after encephalographic examination. Note the generalized deep and superficial cerebral atrophy in *A* and the subdural cap in *B*, with almost complete disappearance of subarachnoid air.

Therefore, gas may pass through the intracranial arachnoid into the subdural space. However, such observations do not indicate whether the gas passes through an intact or through a lacerated membrane.

3. It is not infrequent during craniotomy in cases of elevated cerebrospinal fluid pressure to observe the cerebrospinal fluid exuding through the exposed and distended arachnoid. If fluid can pass through the arachnoid, it is not unreasonable to assume that gas would pass through even more readily. However, after

craniotomy the support afforded the arachnoid by the bone and dura has been removed. The outer surface of the arachnoid is subjected to atmospheric pressure, while the inner surface is subjected to the greater cerebrospinal fluid pressure. In addition, distention of the membrane might cause it to become more permeable, or might even produce minute crevices.

The physical factors in the pneumoencephalographic procedure are different from those which exist during a craniotomy. Because of the intact bone and dura there is no opportunity for the arachnoid to stretch. This lessens the possibility of gas passing through it. Likewise, when the arachnoid is firmly applied to the dura and the latter to the bone little space exists into which gas might escape. On the other hand, when the cerebrospinal fluid cushion is removed from the base of the brain by substitution of a gas the weight of the brain tends to pull it downward, dragging with it the pia and arachnoid (fig. 2). There is therefore a tendency for the upper parts of the potential subdural space to become an actual space. Under such circumstances a subatmospheric pressure probably exists in the subdural space and a positive pressure in the subarachnoid space. Such a situation would facilitate the passage of gas from the subarachnoid to the subdural space.

In order to ascertain whether a gas can pass through an intact arachnoid, pieces of human arachnoid obtained at operation or soon after death were subjected to various gases and pressures in a simple pressure chamber (fig. 8). This was so constructed that one surface of the sample of arachnoid could be exposed to gas in *A* at a given pressure (*Pa*) while the other side was in contact with physiologic solution of sodium chloride in *B* at any other pressure (*Pb*). Pressures could be independently adjusted on either side of the arachnoid by means of a reservoir (*C*). The membrane itself was visible (*1*), and any escaping gas was collected in the neck of the fluid chamber (*B*). All experiments were performed at room temperature. No correction was made for barometric pressure, as pressures in both chambers were relative to the existing barometric pressure. Various gases were used, as well as various differences in pressure. In experiments with carbon dioxide and oxygen the gas was introduced into both chambers several days before an experiment. An equilibrium between the gas and the solution of sodium chloride was thus established, diminishing any chance of dissolving the gas in the solution of sodium chloride should it pass through the membrane.

Samples of arachnoid were obtained from various locations. As the purpose of the experiments was to discover whether a gas could be forced through the intact arachnoid, specimens of "dead" membrane obtained at autopsy were considered likely to prove this point. If the "dead" membrane was impermeable to gas it was considered unlikely that the living membrane would be permeable. In all but 3 cases the arachnoid was presumably "normal," as judged by its appearance and the absence of any meningeal or cerebral pathologic lesions at autopsy. In the first case the arachnoid had been fixed in formaldehyde for several months before use. In the second a deep cerebral tumor had been removed, 5 cm. from the place where the sample of arachnoid was taken. In the third case the sample came

from an area near an old arteriosclerotic cortical thrombosis. These "pathologic" samples reacted to gas under pressure in the same fashion as did the "normal" samples, except that the formaldehyde-fixed specimen was the only one to rupture under pressure. All samples were from men, except 2 from women and 1 from a boy. The arachnoid was taken from the posterior cerebellar recess, area 4, the superior, inferior and lateral parietal cortex, the occipital cortex and the inferior cerebellar hemispheres. All samples, except 1 formaldehyde-fixed specimen, stretched to remarkable degrees under pressure without rupture.

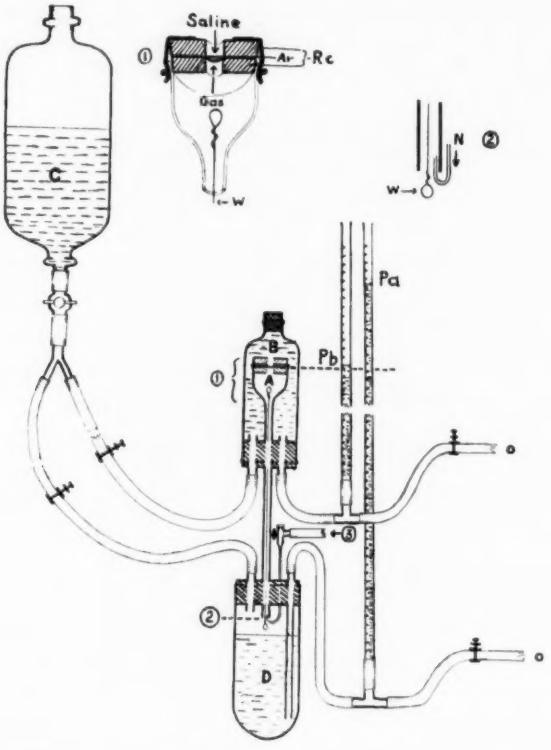

Fig. 8.—Arachnoid pressure chamber.

All chambers are of glass, the stoppers of rubber. Chamber *B* is removed from its supporting stopper. The double stoppers *(Rc)* are removed from chamber *A*, and a sample of arachnoid *(Ar)* is cemented between them, with a piece of open-work gauze on its upper surface to prevent stretching. Chambers *D* and *A* are filled with physiologic solution of sodium chloride from reservoir *C*. The stoppers and the arachnoid are cemented over chamber *A*, without allowing any bubbles to collect under the membrane or stopper. The small stopper is removed from bottle *B*, which is replaced on its supporting stopper to form chamber *B*. Chamber *B* is now filled with physiologic solution of sodium chloride from reservoir *C* and the small cork replaced in such a fashion that no gas is present in the neck of the chamber. By use of a syringe and the outlets *O*, any given gas is introduced through the bent needle *(3* and *N)* into chamber *A*, from which escape of fluid is facilitated by a wire, *W*. By means of appropriate manipulation of reservoir *C*, inlet *3* and outlets *O*, the pressures within *A (Pa)*, below the arachnoid, and within *B (Pb)*, above it, may now be adjusted to any desired levels.

In none of the 17 experiments on 10 samples was it possible to force air, oxygen or carbon dioxide through an intact specimen of human arachnoid under pressures ranging from 150 to 450 mm. of physiologic solution of sodium chloride (0.21 to 0.63 pound per square inch) maintained from twelve to one hundred and twenty hours. These pressures are greater than any which occur during pneumoencephalographic examination.

It might be said that gas could more readily pass through the arachnoid in vivo than in vitro, because of the larger areas of membrane exposed. This is unlikely, as each equivalent area would be subjected to the same volume at the same pressure. The added area exposed merely increases the possibility of additional lacerations or of utilization of some, as yet undiscovered, anatomic aperture in the arachnoid. It is conceivable that the arachnoid in vivo exerts a "selective secretory" action. No evidence of this has been reported.

Therefore these experiments indicate that it is unlikely that air, oxygen, carbon dioxide or nitrogen is capable of passing from the subarachnoid space through an intact arachnoid into the subdural space during the course of or subsequent to pneumoencephalographic examination. As a corollary, it is apparent that when a gas effects an intracranial transfer from the subarachnoid to the subdural space it does so through a lacerated or eroded arachnoid.

SIGNIFICANCE OF SUBDURAL GAS

In the five years between 1933 and 1939, approximately 400 encephalograms were made in this clinic. Forty-seven encephalograms, taken in 42 cases, contained subdural air. In 3 cases subdural shadows occurred only in the second set of roentgenograms, taken twenty-four hours after the encephalographic examination. In 4 cases the air was entirely subdural, owing to its mode of introduction. These 7 cases are excluded from the following analysis except when specifically mentioned. Therefore in this clinic the incidence of subdural air during the encephalographic procedure is approximately 8.7 per cent.

Three random control series were selected from the cases of patients admitted during the same years. These consisted of 50 neuromedical and 50 neurosurgical cases in which no encephalograms were taken and 50 cases in which the encephalograms showed no evidence of subdural air. Comparison of the general trend in all cases of patients admitted with that in cases in which encephalograms were taken indicated that both the cases in which the encephalogram showed subdural air and those in which it did not were representative examples of the total group. The number of cases, however, is too small to permit definite conclusions. In the table is summarized an analysis of the various groups. The predominant pathologic lesion was determined by a study of the cases without reference to the encephalograms.

Encephalograms were made with equal frequency in cases of posttraumatic syndromes following cranial trauma and in cases of disorders

following intracranial injuries at birth. It is therefore significant that in 51 per cent of the cases in which subdural air was present the disturbance followed "cranial injuries" and that in only 6 per cent it followed "birth injuries." In the other groups no significant differences occurred between the cases in which there was "subdural" and those in which there was "subarachnoid" air. Except for the cases of post-traumatic disorders, subdural air occurred most frequently in cases of idiopathic epilepsy (17 per cent). On the other hand, 22 per cent of the encephalograms without evidence of subdural air were obtained from epileptic patients. Of the total group of patients with seizures,

Comparison of 35 Cases in Which Subdural Encephalographic Air Was Present and a Random Series of 50 Cases in Which It Was Absent, Based on the Predominant Physiologic Change in the Central Nervous System

	Average Age, Yr.	Percentage of Males	Predominant Pathologic Lesion, % of Cases							
			"Cranial Injury"	"Birth Injury"	"Vascular Injury"	Tumor	Inflammation	"Epilepsy"	Degeneration	Psychogenic
50 control cases in which no subdural encephalographic air was shown.....	27	50	28	28	0	4	6	22	8	4
35 cases in which subdural encephalographic air was shown										
A. 15 cases in which only hemispheric subdural air was shown.....	31	33	53	13	0	0	0	20	7	7
B. 13 cases in which hemispheric and subtentorial subdural air was shown	31	69	54	0	0	7.5	7.5	16	7.5	7.5
C. 7 cases in which only subtentorial subdural air was present.....	34	57	43	0	14	14	14	14	0	0
D. Total (28) cases in which hemispheric subdural air was shown.....	31	50	54	7	0	3.5	3.5	18	7	7
E. Total (20) cases in which subtentorial subdural air was shown.....	..	63	48	0	7	11	11	15	4	4
F. Total (35) cases in which subdural air was shown.....	32	51	51	6	3	6	6	17	6	5

subdural air occurred in only 9.6 per cent, or in only 3.8 per cent if those with post-traumatic epilepsy are excluded.

Injuries to the head most frequently damage the meninges and cerebral surfaces. The arachnoid membrane is primarily involved in the resultant lacerations, hematomas, adhesions or contusions. A damaged arachnoid may be more liable to rupture during the encephalographic procedures. "Birth injuries," on the other hand, are usually deep cerebral lesions, and as such are least likely to involve the arachnoid. The frequent occurrence of subdural air in cases of post-traumatic syndromes is therefore to be expected. When present, it suggests that the arachnoid has been damaged.

Although subdural air, when it occurs, is found most frequently in cases of post-traumatic disturbances, it is not a frequent finding in

the post-traumatic group as a whole, occurring in not more than 20 per cent of the total number of cases. The diagnostic value of subdural air is doubtful. Of 13 cases in which the pathologic condition was proved and in which subdural air was present, the encephalograms were of proved diagnostic value in 3—2 cases of adhesions and 1 of subdural hematoma.

Five cases of proved subdural hematomas occurred in this series, in only 1 of which was the conformation of the subdural air *diagnostic* of the hematoma. It has been shown in a previous study [10] that subdural air was present in 5 of 18 cases of subdural hematomas (28 per cent) and in 1 of 4 cases in which the lesion was suspected but was proved not to be hematoma. "It is therefore apparent that subdural air over the hemispheres may be associated at times with subdural hematomas, but does not have any great diagnostic significance." [10] When encysted or when outlining a mass subdural air is of diagnostic value.[14]

Subdural air which appears twenty-four hours after the encephalographic examination is probably of no diagnostic value. No worth while study has as yet been published which attributes any special significance to this type of subdural air. As a roentgenogram [15] is made only rarely as a check on the second day in this clinic, the 4 cases in which subdural air shadows of this type appeared are of no statistical significance. After the encephalographic examination, the fluid cushion of the brain has been largely removed. The amount of stretch and distortion to which the arachnoid is subjected by the unsupported shifting brain during convalescene might easily tear a normal arachnoid. Subdural air occurs more frequently (in 25 per cent of cases) in clinics in which active cranial manipulation is practiced during the injection of air.[1] It must be remembered that after replacement of cerebrospinal fluid by a gas the soft brain mass is for a time in a "dry box." The full effects of gravity, inertia and motion are then transmitted to the brain. As the brain is "hanging from the veins," which leave the cortex to enter the sinuses, the arachnoid at these areas is subject to a great deal of stress (fig. 2). It is probable that most tears occur in the neighborhood of these emergent veins, or at the pacchionian granulations, as suggested by Howard.[16]

It is suggested that air gains entry to the subdural space in the same manner in cases of post-traumatic injury. In such cases dural-arachnoid

14. Dyke, C. G., and Davidoff, L. M.: Chronic Subdural Hematoma: A Roentgenographic and Pneumencephalographic Study, Bull. Neurol. Inst. New York **7**:112 (Sept.) 1938. von Storch and Munro.[10] Holt and Pearson.[8]

15. Pendergrass, E. P.: Encephalography: Value of Second Day Examination, Radiology **26**:146 (Feb.) 1936.

16. Howard, C.: Observations on Encephalography, Am. J. Roentgenol. **32**:301 (Sept.) 1934.

adhesions probably cause more tears than do the normal emergent veins. The presence of such post-traumatic meningeal adhesions accounts for the higher incidence of subdural air in cases of post-traumatic disturbance, and at the same time explains why air shadows of this type are not diagnostic of subdural hematomas.

In 4 cases encephalographic examination was repeated at a later date. In 1 case the first encephalogram showed nothing but subdural air of the type found after lumbar subdural injection. When the procedure was repeated a week later, with both needles in the subarachnoid space, no subdural air appeared. This confirmed the previous impression that the subdural air had been directly injected into the lumbar subdural space. In a second case two encephalograms made within a week of each other showed combined ventricular, subarachnoid and subdural air in the same locations. This suggests that the arachnoid fistula produced at (or preceding) the taking of the first encephalogram was still patent one week later.

In the remaining 2 cases there was an interval of three years between taking the encephalograms. In both instances subdural air was found after each procedure, but in entirely different areas (shifting from the right to the left and from the right hemisphere to the subtentorial region, respectively). In 1 case post-traumatic hysteria was not relieved by either injection of air. In the second case a patient with postencephalic (and meningeal) epilepsy had a remission of one year after each encephalogram was taken. These cases suggest that a pathologic arachnoid was present in both instances, but that new fistulas were opened during each procedure.

Subtentorial subdural air occurred alone in only 7 cases, or 20 per cent, of this series, and was combined with hemispheric subdural air in 37 per cent. When it occurs alone it is apparently of little diagnostic value, although it does occur more frequently in cases of post-traumatic disorders (table). Its mode of entry into the subtentorial subdural space has not been determined. The means may be similar to that already described.

Gas introduced directly into the lumbar subdural space (in 3 of 42 cases in this series) is of no diagnostic value per se. It may, however, outline subdural masses, and under such circumstances would be valuable. A practical technic for lumbar subdural injection of air should be most useful in the diagnosis and treatment of the post-traumatic encephalopathies and psychoses, as well as in the diagnosis and drainage of fluid subdural hematomas. Cranial subdural insufflation has been successfully performed.[4] Lumbar insufflation has as yet been purely accidental.

It is suggested that the following technic may be of value:

A lumbar puncture is performed in the usual manner while the patient is in the left lateral recumbent position. With the needle left in place, the patient's hips are elevated and the shoulders depressed, as for caudal myelographic examination.[17] All obtainable cerebrospinal fluid is removed. A second puncture is then performed in an adjacent intervertebral space, while the patient remains in the same position. The stylet is removed from the needle after the vertebral ligaments are punctured, and the needle introduced further with great care, until the dura has been pierced. A syringe is then used to determine whether fluid is obtainable and whether air may be readily injected. If no fluid is obtained and air may be readily injected, it is assumed that the tip of the needle lies in the subdural space created by retraction of the collapsed caudal arachnoid. The patient is carefully placed in the sitting position, and replacement of subarachnoid fluid by subdural gas is continued, as in the double puncture simultaneous replacement encephalographic procedure.[11]

CONCLUSIONS

1. Intracranial subdural gas shadows occur in from 7 to 20 per cent of cases in which the pneumoencephalographic procedure is performed by the lumbar route.

2. They occur more frequently when active cranial manipulation is part of the technic.

3. The shadows are characteristic and may be readily identified.

4. A gas may enter the intracranial subdural space during lumbar encephalographic examination (*a*) by direct introduction into the lumbar subdural space or (*b*) through tears in the arachnoid which have occurred before, during or after the examination.

5. Air or its constituent gases cannot be made to pass through the human arachnoid at a pressure of 450 mm. of water (0.627 pound per square inch) maintained in vitro for seventy-two hours.

6. It is unlikely that these gases pass through an intact arachnoid in vivo as a result of the encephalographic procedure.

7. The presence of subdural air in an encephalogram, when not introduced by way of the lumbar subdural space, implies that the arachnoid has been torn and suggests that the membrane has been involved in a superficial pathologic process.

8. Subdural gas occurs most frequently in patients who have been subjected to cranial injuries.

9. Although often associated with cranial injury, and occasionally with subdural hematomas, subdural gas is diagnostic of neither.

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17. Coggeshall, H. C., and von Storch, T. J. C.: Diagnostic Value of Myelographic Studies of the Caudal Dural Sac, Arch. Neurol. & Psychiat. **31**:611 (March) 1934.

EFFECT OF EPINEPHRINE ON CONVULSIONS

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In a previous paper Darrow and Gellhorn [1] showed that epinephrine in physiologic concentrations produces inhibitory effects on both branches of the autonomic nervous system. It was shown that in the presence of epinephrine the sympathetic responses of the pupil, blood pressure, nictitating membrane and foot pads (galvanic reactions) are reduced, and that the responses involving inhibition of the parasympathetic constrictor tonus of the sympathectomized eye are increased. The close association of sympathetic discharges with convulsions produced by insulin (Gellhorn [2]) and metrazol (Gellhorn and Darrow [3]) made it desirable to investigate whether the inhibitory effects of epinephrine extend to the somatic nervous system and lead to diminution or suppression of the convulsions. Such an investigation is particularly indicated because of the report by Hall and Leibel [4] that epinephrine increases metrazol convulsions and the finding of Schweitzer and Wright [5] that it inhibits the knee jerk.

METHODS

Insulin and metrazol convulsions were studied in 24 waking and anesthetized rabbits and the results further analyzed in 15 anesthetized cats which were arranged

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1. Darrow, C. W., and Gellhorn, E.: Inhibitory Effects of Adrenalin on Autonomic Function, Proc. Soc. Exper. Biol. & Med. **40**:487-488, 1939; Am. J. Physiol. **127**:243-251, 1939.

2. Gellhorn, E.: Effects of Hypoglycemia and Anoxia on the Central Nervous System: A Basis for a Rational Therapy of Schizophrenia, Arch. Neurol. & Psychiat. **40**:125-146 (July) 1938.

3. Gellhorn, E., and Darrow, C. W.: The Action of Metrazol on the Autonomic Nervous System, Arch. internat. de pharmacodyn. et de thérap. **62**:114-128, 1939.

4. Hall, G. E., and Leibel, B.: Physiological Studies in Experimental Insulin and Metrazol Shock: V. Effect of Autonomic Drugs on Metrazol Convulsions, Am. J. Psychiat. **95**:553-566, 1938.

5. Schweitzer, A., and Wright, S.: The Action of Adrenalin on the Knee Jerk, J. Physiol. **88**:476-491, 1937.

for the mechanical registration of convulsions and blood pressure. Epinephrine hydrochloride was injected intravenously in concentration of from 1:100,000 to 1:150,000 of freshly prepared solution. Sugar determinations were made by the Shaffer-Hartman method.

RESULTS

Effect of Epinephrine on Convulsions of Insulin Hypoglycemia in the Rabbit.—Eight rabbits were given injections of 2.5 units of insulin [6] per kilogram of body weight. When clonic-tonic convulsions appeared, from 2 to 3 cc. of epinephrine hydrochloride in concentration of 1:100,000 or 1:150,000 (0.006 to 0.02 mg. per kilogram) was injected intravenously. Following the injection, one of us who held the animal observed almost immediately a relaxation of the extremities. The epinephrine consistently (in 8 rabbits) caused the tonic component of the convulsions to disappear completely, and either great reduction in the clonic movements or complete cessation of convulsions resulted. Most striking is the fact that this recovery occurred in the absence of return of the normal blood sugar level. Dextrose determinations at this time gave values varying between 12 and 24 mg. per hundred cubic centimeters of blood. The duration of this recovery varied greatly. After from two to twenty minutes typical clonic-tonic convulsions recurred and could again be stopped or alleviated by epinephrine. The results of a typical experiment may be reported.

Rabbit, weighing 1.56 Kg. 2:21 p. m.: Insulin, 2.5 units per kilogram, subcutaneously.

3:43 p. m.: Severe clonic-tonic convulsions with opisthotonos. Injection of 0.03 mg. of epinephrine hydrochloride into ear vein. Immediate relaxation of extremities. Animal got up and ran to a corner of the laboratory. Perfect coordination of movements.

3:46 p. m.: Animal still normal. Blood sugar 24.1 mg. per hundred cubic centimeters.

4:02 p. m.: Severe tonic-clonic convulsions.

4:03 p. m.: Epinephrine hydrochloride, 0.03 mg., again injected into ear vein. Rabbit sat up immediately; convulsions completely stopped.

4:15 p. m.: Convulsions. Injection of 30 cc. of 10 per cent solution of dextrose intraperitoneally; convulsions stopped.

The observations were similar to those of Geiger and Szirtes,[7] who found that hypoglycemic convulsions induced by atropine or starvation in splanchnicotomized rabbits could be alleviated by epinephrine, although the blood sugar remained at a convulsive level.

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6. Insulin was supplied by Eli Lilly & Co., Indianapolis, and metrazol, by the Bilhuber-Knoll Corporation, Orange, N. J.

7. Geiger, E., and Szirtes, L.: Maximale Hypoglykämie ohne Insulin-Anwendung, Arch. f. exper. Path. u. Pharmakol. **119**:1-23, 1927.

Effect of Epinephrine on Metrazol Convulsions in the Rabbit.—Similar experiments were carried out on 14 rabbits which received metrazol intravenously. Most animals were slightly narcotized with ethyl carbamate (0.8 Gm. per kilogram). While the intensity and duration of the convulsions varied greatly, numerous experiments indicated that epinephrine in physiologic concentrations typically decreases or inhibits metrazol convulsions. The relaxing influence on the tonus of the extensors of the extremities and of the head was well marked.

Rabbit, weighing 2.92 Kg. Ethyl carbamate, 1 Gm. per kilogram, injected subcutaneously. Animal not fully narcotized, held head up.

10:47 a. m.: Metrazol, 60 mg. per kilogram, given intravenously. Immediate severe clonic-tonic convulsions.

10:48 a. m.: Epinephrine hydrochloride, 0.023 mg. (0.0079 mg. per kilogram), injected intravenously. Immediate flaccidity; occasional twitches of head and forelegs.

10:52 a. m.: Clonic movements began to recur. Extensor tonus increased also until, at 10:57 a. m., typical clonic-tonic convulsions were present.

10:57½ a. m.: Epinephrine hydrochloride, 0.03 mg. (0.01 mg. per kilogram), given intravenously.

10:58 a. m.: Tonus normal. No convulsions. Pupils maximally dilated.

11:00 a. m.: Animal still relaxed, occasional twitches. No convulsions.

11:02 a. m.: Clonic movements. Tonus of extremities increased.

11:19 a. m.: Clonic convulsions, 10 to 12 per minute.

11:23 a. m.: Epinephrine hydrochloride, 0.03 mg. (0.01 mg. per kilogram), injected intravenously.

11:24 a. m.: Extremities completely relaxed; no convulsions. Animal remained normal.

The antagonistic action of epinephrine is not restricted to its effects on convulsive movements induced by metrazol, but applies to the general state of activity. It is well known that metrazol has a marked antagonistic action toward barbiturates (Hildebrandt [8]). If rabbits previously narcotized with soluble barbital U. S. P. are given injections of metrazol, they may not show convulsions but are aroused to normal activity and show normal righting reflexes if an attempt is made to place them on one side. If such an animal is given injections of 0.01 to 0.015 mg. per kilogram of epinephrine hydrochloride, it immediately loses this activity and after one or two minutes lies on its side in a semistuporous state and shows no righting reflexes.

Other types of somatic activity are similarly influenced by minute amounts of epinephrine. Cats narcotized with chloralosane (a com-

8. Hildebrandt, F.: Pentamethylenetetrazol (Metrazol), in Heffter, A.; Heubner, W., and Schüller, J.: Handbuch der experimentellen Pharmakologie, Berlin, Julius Springer, 1937, vol. 5, pp. 151-183.

pound of chloral hydrate and dextrose) or ethyl carbamate plus chloralosane show frequently a strychnine-like condition. Slight mechanical stimuli elicit widespread reflexes. Injection of epinephrine may reduce irritability to normal.

Marked nystagmus-like movements of the eyes observed after the injection of physostigmine, as mentioned by Grinker and Serota,[9] disappear after injection of 0.005 to 0.007 mg. of epinephrine hydrochloride per kilogram of body weight.

Head nystagmus was observed after metrazol in 1 instance and was temporarily stopped by epinephrine (0.005 mg. per kilogram).

That epinephrine secreted within the animal may also serve an anticonvulsant function is indicated by a variety of observations. The duration of convulsions produced by a standard dose of 0.5 cc. of 10 per cent metrazol in 1 instance was prolonged from four minutes before ligation of both adrenal veins to nine minutes after ligation. In another animal in which the adrenal veins were tied 0.5 cc. of 10 per cent metrazol produced convulsions, and when these convulsions had ceased faradic stimuli applied to the brachial plexus for fifteen seconds with the coil at 5 cm. served to reprecipitate the seizure. Immediately thereafter, on releasing one of the adrenal veins, neither repetition of the dose of metrazol nor of the faradic stimulus was sufficient to cause convulsions.

Role of the Buffer Nerves in Inhibitory Action of Epinephrine on the Somatic Nervous System.—These inhibitory effects of epinephrine are found to be intimately related to the effect of the drug in raising the blood pressure. The inhibition is found typically to occur during the period of high blood pressure, and the convulsions often tend to recur, or even to be augmented, during the subsequent period of fall in blood pressure. Convulsions have even been terminated by raising the blood pressure with Ringer solution. They have in some instances been precipitated in excitable animals by lowering the blood pressure with amyl nitrite.

A series of experiments was carried out on 15 narcotized cats (0.6 Gm. per kilogram of ethyl carbamate intraperitoneally plus 30 mg. per kilogram of chloralosane intravenously or 100 mg. per kilogram of chloralosane subcutaneously or 45 mg. per kilogram of pentothal [sodium ethyl 1-methylbutylthiobarbiturate] intraperitoneally) in order to study the inhibitory action of epinephrine quantitatively and to investigate the role of blood pressure and of the buffer nerves in this process. The convulsions were recorded from the right hindfoot by means of a pulley and two Marey tambours. The blood pressure was recorded from the left carotid artery by means of a Hürthle manometer.

9. Grinker, R. R., and Serota, H. M.: Studies on Corticohypothalamic Relations in the Cat and Man, J. Neurophysiol. **1**:573-589, 1938.

Figure 1 shows the influence of 0.02 mg. of epinephrine hydrochloride on metrazol convulsions in the narcotized cat. Although the blood pressure rises only to a moderate degree, the convulsions are almost completely inhibited. Shortly after the end of the infusion and simultaneously with the fall of the blood pressure to the original level the convulsions reappear. This phenomenon was constant provided the convulsions were not too severe.

Since it is known (Heymans and his associates [10]) that epinephrine affects the vagus nerve and the respiratory center solely by way of the carotid sinus and since Spychala [11] showed an inhibitory action on the knee jerk and Koch [12] an inhibition of spontaneous movements resulting from increasing the pressure in the carotid sinus, it was desirable to determine to what extent the inhibition of convulsions by epinephrine is due to its action on the buffer nerves. Therefore,

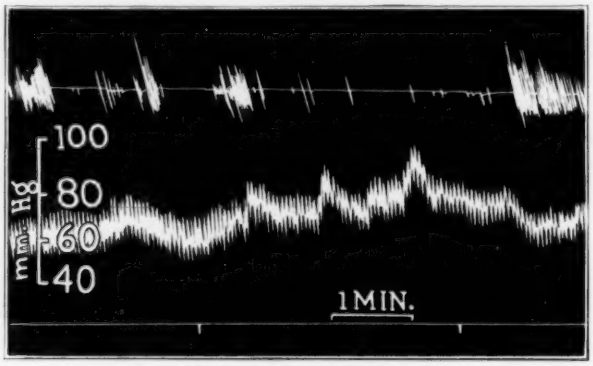

Fig. 1.—Cat, weighing 2.5 Kg., narcotized with 50 mg. per kilogram of chloralosane given subcutaneously plus 50 mg. per kilogram injected intramuscularly. Records from above downward are those of convulsions from the right hindleg, blood pressure from the carotid artery (Hürthle manometer) and signal, showing the period of injection of 3 cc. of epinephrine hydrochloride, 1 : 150,000 (0.008 mg. per kilogram).

experiments were carried out in which, after demonstrating the inhibitory action of epinephrine on the normal narcotized animal, the buffer mechanisms were partially or completely eliminated. Chloralosane anes-

10. Heymans, C.; Bouckaert, J. J., and Régniers, P.: Le sinus carotidien et la zone homologue cardio-aortique: Physiologie, pharmacologie, pathologie, clinique, Paris, Gaston Doin & Cie, 1933.

11. Spychala, W.: Ueber den Einfluss der pressorezeptorischen Reflexerfolge auf die Aktionsströme von Skelettmuskeln, Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch., 1933, pp. 140-144.

12. Koch, E.: Die Irradiation der pressorezeptorischen Kreislaufreflexe, Klin. Wchnschr. **11**:225-227, 1932.

thesia was used exclusively, since it best maintains the reflexes of the buffer nerves (Heymans and Bayless [13]).

The results are illustrated by some typical experiments. Figure 2 *A* to *C* shows the effect of epinephrine on metrazol convulsions after the carotid sinuses had been removed bilaterally. The vagus nerves were intact. At points *A* and *C*, 100 mg. of metrazol is injected intravenously and elicits severe convulsions, in which the individual clonic-tonic spasms follow each other closely. Between these two tests the same amount of metrazol is injected, followed immediately by 0.013 mg. of epinephrine hydrochloride, with the result that only a few twitches

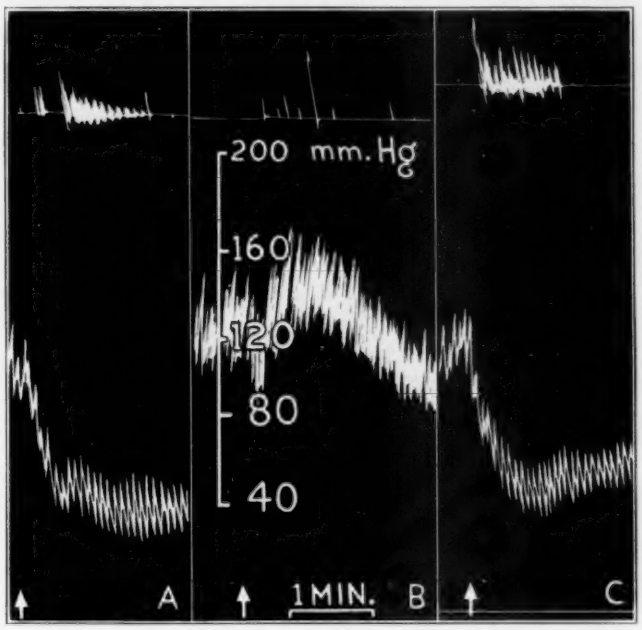

Fig. 2.—Cat, weighing 2.6 Kg., narcotized with 100 mg. of chloralosane per kilogram given subcutaneously. Both carotid sinuses were denervated; the vagus nerves were intact. At *A* and *C*, 1 cc. of 10 per cent metrazol was given intravenously. At *B*, 1 cc. of 10 per cent metrazol plus 2 cc. of epinephrine hydrochloride, 1 : 150,000 (0.005 mg. per kilogram), were given intravenously.

occur (fig. 2 *B*). It is to be noted that the concomitant injection of epinephrine greatly modifies the typical blood pressure curve produced by metrazol (Gellhorn and Darrow [3]). Whereas at *A* and *C* in figure 2 the blood pressure falls very rapidly after the injection of metrazol, it rises when epinephrine is simultaneously injected (fig. 2 *B*).

13. Heymans, C., and Bayless, F.: Influences de l'anesthésie par la morphine-pernoctone ou par la chloralosane sur la pression artérielle et sur les reflexes vasomoteurs de la régulation proprioceptive de la pression artérielle, Arch. internat. de pharmacodyn. et de thérap. **56**:419-426, 1937.

A similar experiment is illustrated in figure 3 *A* to *C*, in which, however, only one vagus nerve had been left intact. The experimental procedure was similar to that shown in figure 2. Epinephrine here completely inhibits the metrazol convulsions, although in the preceding and following control experiments (without epinephrine) convulsions were elicited. It is again worthy of note that the fall of blood pressure accompanying the metrazol convulsions at *A* and *C* in figure 3 is completely absent when epinephrine is given immediately after the metrazol fig. 3 *B*).

A final series of experiments was performed on animals with denervation of both carotid sinuses and section of both vagus nerves.

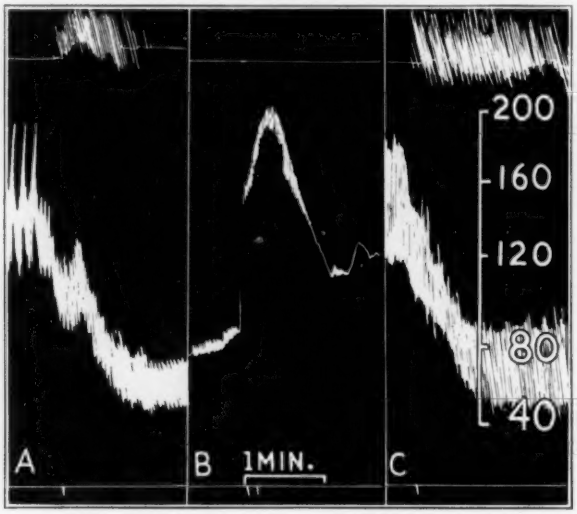

Fig. 3.—Cat, weighing 2.8 Kg., narcotized with 100 mg. of chloralosane per kilogram given subcutaneously. Both carotid sinuses were denervated; one vagus nerve was cut. At *A* and *C*, 0.75 cc. of 10 per cent metrazol was given intravenously. At *B*, 0.75 cc. of 10 per cent metrazol, followed (at second mark) by 2 cc. of epinephrine hydrochloride, 1 : 150,000 (0.0047 mg. per kilogram), was injected intravenously.

The result of experiments carried out on such "denervated" cats was in sharp contrast to those already described. In no instance was an inhibitory action of epinephrine observed in the "denervated" animal.

Figure 4 shows two experiments carried out in succession on the same cat and illustrates the various types of responses which may be found. The first record shows a slight increase in the convulsions during the rise of blood pressure from injection of 0.02 mg. of epinephrine hydrochloride, whereas in the second record the convulsions remain unaltered during the rise in blood pressure. Similar results were

obtained in other animals under the same conditions. The increase in frequency or intensity of the convulsions was, however, never great and was frequently absent. The other characteristic feature of the effect of epinephrine on the denervated cat is the greatly increased convulsive discharge when the blood pressure falls. If the pressure attains a lower level than that just prior to the injection of epinephrine the temporary increase in convulsions may be considerable, as in the second record of figure 4.

Experiments prove conclusively that the inhibitory action of epinephrine on convulsions is dependent on the buffer nerves. The inhibition may occur after removal of both carotid sinuses so long as

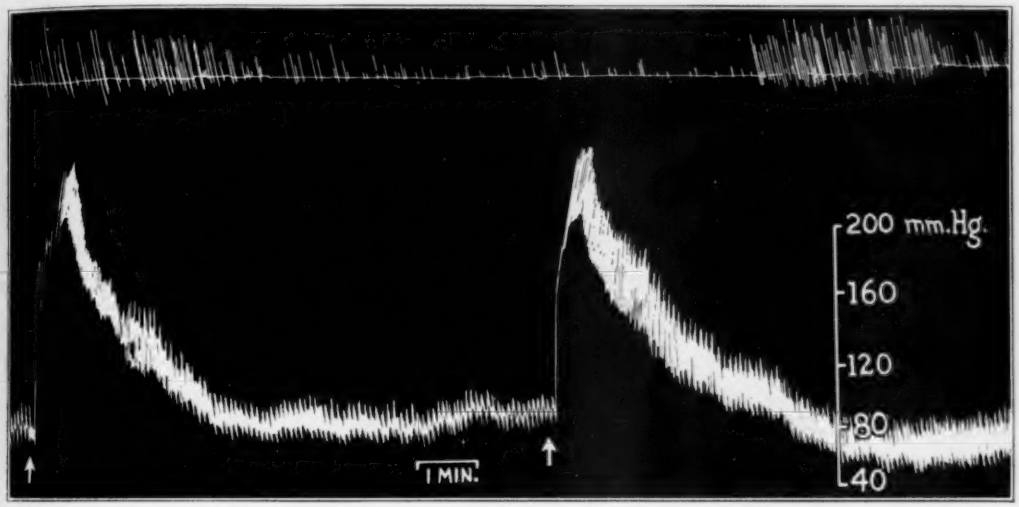

Fig. 4.—Cat, weighing 2.8 Kg., narcotized with 100 mg. of chloralosane given subcutaneously. The carotid sinuses were denervated, and the vagi nerves were cut. At the point marked by the arrow 3 cc. of epinephrine hydrochloride, 1 : 150,000 (0.0071 mg. per kilogram), was given intravenously.

one vagus nerve is intact. After section of the last buffer nerve, however, epinephrine is either without effect on the convulsions or has a reversed effect.

COMMENT

Taking into account the work (Darrow and Gellhorn [1]) on the inhibitory action of epinephrine on the autonomic nervous system, it may be said that in the normal animal small doses of epinephrine hydrochloride (0.004 to 0.015 mg. per kilogram) inhibit functions of both the autonomic and the somatic nervous system. The experiments presented in this paper show this with respect to various activities of the somatic nervous system. It is shown in the case of convulsions

induced by different drugs (insulin, metrazol) and also for the nystagmic movements following physostigmine and for the state of hyperreflexia sometimes observed in animals under anesthesia, especially that induced with chloralosane. The same principle is illustrated by the fact that an animal which has been awakened by metrazol from narcosis produced by soluble barbital may be put to sleep again with epinephrine.

The experiments with cats in which the buffer nerves had been partially or completely eliminated prove that the inhibitory action is due to a reflex via the carotid sinus and depressor nerves. Apparently, either of the two mechanisms is sufficient.

It is important to note that Koch [12] was able to modify the general excitability in non-narcotized monkeys by varying the pressure in the carotid sinus. A rise in pressure resulted in greatly decreased excitability and in decrease of the muscle tonus. These observations and the results of our own studies make it probable that the inhibitory action of epinephrine is due to the effect of increased blood pressure in stimulating the pressure receptors in the carotid sinus and arch of the aorta, since this site of action has been proved with regard to the effect of epinephrine on the vagus center and on respiration (Heymans and his associates [10]). A simultaneous action on the chemoreceptors is, however, by no means excluded. Observations by Haas,[14] if confirmed, would give an even deeper insight into the mechanism of this inhibitory action. This author found that the acetylcholine content of the brain is reduced after epinephrine, but that this effect is abolished after elimination of both carotid sinuses. If it can be assumed that acetylcholine plays a role in the transmission of nervous impulses across the synapses of the somatic nervous system similar to that which has been shown for the autonomic system, the findings of Haas make the inhibitory effect of epinephrine understandable.

The results show clearly that the phenomenon described is fundamentally different from the observation of Schweitzer and Wright [5] that 0.3 to 0.4 mg. of epinephrine hydrochloride inhibits the knee jerk. Not only was epinephrine used, as they pointed out, in unphysiologic amounts (about twenty times as large as those used in our experiments) but the effect was independent of the buffer nerves. In as yet unpublished experiments by Greenberg and one of us (E. G.) on inhibition of the lingual-maxillary reflex of the cat by epinephrine, quantities similar to those found necessary by Schweitzer and Wright in experiments on the knee jerk were required.

The nature of the slight (and not constant) increase in the convulsions during the rise in blood pressure in the denervated animal is hard to explain. The fact that it does not occur regularly makes it probable

14. Haas, H. T. A.: Untersuchungen über die pharmakologische Beeinflussung vegetativer Zentren: II., Arch. f. exper. Path. u. Pharmakol. **192**:117-130, 1939.

that it is the result of altered circulation and that the effect depends on the general circulatory conditions prior to the administration of epinephrine. The prompt and marked increase of convulsions during the fall of blood pressure after epinephrine, particularly when the blood pressure falls to somewhat lower levels than were present before epinephrine was injected, suggests that it is a reflex. Since the carotid sinus and aortic reflexes are eliminated, the effect may be due to the abdominal vasotatic reflexes of Heymans, Bouckaert, Farber and Hsu.[15]

The increase in metrazol convulsions observed by Hall and Leibel [4] and in a small series of experiments by Reiners and Watterott [16] seems to us of greater pharmacologic than physiologic significance because these investigators employed relatively large doses of epinephrine (0.05 mg. per kilogram). We have obtained similar aggravation of convulsions with large doses. Relatively large concentrations of epinephrine increase the frequency and intensity of the electrical discharge (Grinker and Serota [9]) and may lead to an increase in convulsions, whereas smaller concentrations inhibit them.

Although our investigations are primarily of a physiologic character, some possible applications of these studies may be mentioned. A survey of the literature shows that the experimental study of epilepsy has primarily been concerned with the effects of various convulsants (Pike and his associates [17] and Lennox and Cobb [18]), the neurologic mechanisms of the experimentally produced convulsions (Pike and his associates [19] and Pollock and Davis [20]) and the physiologic factors which may dispose to seizures (McQuarrie and his co-workers [21] and Fay [22]). So far as anticonvulsants are concerned, the studies in general concern attempts to find effective drugs and to analyze their action in clinical

15. Heymans, C.; Bouckaert, S.; Farber, S., and Hsu, F.: Spinal Vasomotor Reflexes Associated with Variations in Blood Pressure, Am. J. Physiol. **117**:619-625, 1936.

16. Reiners, H., and Watterott, A.: Die Bedeutung der Schilddrüse in der Genese epileptiformer Krampfzustände, Ztschr. f. d. ges. exper. Med. **103**:750-755, 1938.

17. Pike, F.; Elsberg, C.; McCulloch, W., and Rizzolo, A.: Some Observations on Experimentally Produced Convulsions, Am. J. Psychiat. **9**:259-283, 1929.

18. Lennox, W., and Cobb, S.: Epilepsy, Medicine **7**:105-290, 1928.

19. Pike, F. H.; Elsberg, C. A.; McCulloch, W. S., and Chappell, M.: The Problem of Localization in Experimentally Induced Convulsions, A. Research Nerv. & Ment. Dis., Proc. **7**:203-230, 1929.

20. Pollock, L., and Davis, L.: Experimental Convulsions, A. Research Nerv. & Ment. Dis., Proc. **7**:158-175, 1929.

21. McQuarrie, I.; Husted, C., and Manchester, R.: The Effect of Induced Changes in the State of Hydration upon the Occurrence of Seizures in Epileptic Children, A. Research Nerv. & Ment. Dis., Proc. **7**:623-637, 1929.

22. Fay, T.: The Therapeutic Effect of Dehydration on Epileptic Patients, A. Research Nerv. & Ment. Dis., Proc. **7**:592-622, 1929.

or experimental epilepsy.[23] The fact that minute quantities of epinephrine and variations in the amount of epinephrine secreted by the adrenal glands definitely influence metrazol and insulin convulsions deserves the attention of the investigators of human epilepsy. Two possibilities suggest themselves: first, that the amount of epinephrine present in the blood is less in epileptic than in normal persons, and, second, that epinephrine, if present in normal quantities, inhibits the somatic nervous system to a lesser extent in epileptic persons. The carotid sinus and depressor reflexes may be implicated. A satisfactory quantitative determination of epinephrine in the blood must be developed to test this hypothesis.

SUMMARY

1. The intravenous injection of epinephrine hydrochloride in minute quantities (0.004 to 0.015 mg. per kilogram of body weight) diminishes or inhibits temporarily insulin and metrazol convulsions in rabbits, although the blood sugar remains unchanged in the insulin experiments.

2. The injection of epinephrine may induce sleep in rabbits which have been awakened by metrazol from narcosis induced with soluble barbital.

3. Hyperreflexia as seen in cats under chloralosane anesthesia is abolished by epinephrine.

4. Experiments on narcotized cats show that the anticonvulsant action of epinephrine is linked with carotid sinus and depressor reflexes. The action is abolished by bilateral vagotomy and denervation of both carotid sinuses, but is still present after carotid sinus denervation if one vagus nerve is intact. These facts and the observation that convulsions are frequently increased when the blood pressure is lowered by amyl nitrite make it probable that pressor reflexes from the carotid sinus and arch of the aorta regulate the excitability of the somatic nervous system in a manner similar to that shown by Darrow and Gellhorn for the autonomic system.

5. The increase of metrazol convulsions with epinephrine occurs only with higher concentrations and is therefore of pharmacologic rather than of physiologic significance.

6. The possible application of these findings to the problem of epilepsy is discussed.

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23. Merritt, H. H., and Putnam, T. J.: A New Series of Anticonvulsant Drugs Tested by Experiments on Animals, Arch. Neurol. & Psychiat. **39**:1003-1015 (May) 1938.

ROLE OF ALLERGY IN MULTIPLE SCLEROSIS

INCIDENCE OF ATOPY IN A SERIES OF FORTY CASES

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In recent years attempts have been made to attribute to allergic mechanisms many diverse diseases of unknown pathogenesis. These attempts have occasionally led to sweeping conclusions—conclusions which do not appear to be warranted on the basis of the facts adduced.

Allergic phenomena have been mentioned in connection with a number of neurologic conditions, and it has been suggested that certain of these diseases may be entirely or partially based on allergy, e. g., convulsive states, optic neuritis, encephalopathies, migraine, palsies and multiple sclerosis.

In a few of these conditions there seems to be some clinical or laboratory evidence which justifies the assumption that in at least some cases the disease is associated with states of specific acquired hypersensitivity to foods, drugs, inhalants, or other environmental substances, or foreign serums. In others there is no such evidence, and the suspicion of a relationship is based merely on similarities observed between the course of the neurologic disease and that of certain other diseases known to be based on allergy.

Thus, it seems that the evidence for the allergic nature of multiple sclerosis is based largely on such demonstration of analogies. In 1935 Kennedy alluded to this fact, calling attention to multiple sclerosis and its "episodes, its intermissions, the curability of its most acute crisis, its attack on the optic nerves, its neglect of sensory paths," all of which suggested to him that this condition might be based on allergy. Indeed, several investigators, including Kennedy, have mentioned a few cases of multiple sclerosis or multiple-sclerosis-like syndromes in which exposure to allergens was regarded as having been proved to be responsible for the elicitation of attacks.[1]

From the Department of Dermatology and the Neurologic Division, the Montefiore Hospital for Chronic Diseases.

1. Kennedy, F.: Allergic Manifestations in the Nervous System, New York State J. Med. **36**:469, 1936. Monier-Vinard, de Font-Réaulx, Soulignac and Tsocanakis: Syndrome de sclérose en plaques associé à un urticaire fébrile

(Footnote continued on next page)

As soon as the theory of the allergic nature of multiple sclerosis is given serious consideration, it becomes necessary to study this condition with a view to obtaining objective evidence tending either to include it with or to exclude it from the known categories of allergic disease. For this reason, we undertook to study a large series of patients with multiple sclerosis from the point of view of one of the common, distinctive forms of human allergy, viz., atopic hypersensitivity.[2]

This type of allergy, which is clinically represented by asthma, hay fever and atopic dermatitis, is characterized chiefly by: (1) a high incidence of atopic conditions in the familial as well as in the personal history; (2) wheal responses to scratch and intradermal tests with the "protein" fractions of foods, inhalants and other materials; (3) eosinophilia in the blood, and (4) frequent observation of passive transfer antibodies or reagins (Prausnitz-Küstner reaction).

Atopy is only one of many characteristic forms of allergy known to appear in man (others are, for example, contact allergy, tuberculin allergy and various forms of drug allergy). It is therefore obvious that our present investigation of the presence of the criteria of atopy could shed no light on the possible relationship of multiple sclerosis to any form of allergy other than atopy.

EXPERIMENTAL INVESTIGATION

The work was done on 40 patients. Through permission of Dr. Israel S. Wechsler, 21 patients from the neurologic division of the Montefiore Hospital were placed at our disposal, and 19 were patients of Dr. Richard Brickner.

EXPERIMENT 1.—On all 40 patients, scratch tests were made with from 64 to 70 common food allergens and with 34 common inhalant and other allergens (table). Histories of 30 of the 40 patients were taken with regard to the familial and personal incidence of atopic conditions, the ingestion of drugs and exposure to occupational as well as other environmental substances prior to the onset of the disease. From the remaining 10 patients no exact histories could be obtained.

It was found that of the 30 patients who were studied completely with regard both to history and to skin tests, 7 gave a family history of asthma, hay fever or atopic dermatitis.

Five of these 30 patients had, at one time or another, suffered from hay fever or asthma. These 5 patients all gave definitely positive wheal reactions to scratch tests with foods or inhalants or both.

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récidivant post-sérothérapique: Intolérances médicamenteuses multiples, Bull. et mém. Soc. méd. d. hôp. de Paris **51**:1163, 1935. Putnam, T. J.: Studies in Multiple Sclerosis: Etiologic Factors in Multiple Sclerosis, Ann. Int. Med. **9**:854, 1936.

2. Coca, A. F.; Walzer, M., and Thommen, A. A.: Asthma and Hay Fever in Theory and Practice, Springfield, Ill., Charles C. Thomas, Publisher, 1931. Sulzberger, M. B.; Spain, W. C.; Sammis, F., and Shahon, H. I.: Studies in Hypersensitiveness in Certain Dermatoses, J. Allergy **3**:423, 1932. Sulzberger, M. B., and Goodman, J.: Nomenclature, Definition and Classification of Allergy and Allergic Manifestations, M. Rec. **143**:17, 1936.

Three patients with no personal but a familial history of atopy gave positive wheal reactions to foods and/or inhalants on scratch testing.

Twenty patients had no personal or familial history of atopy. Among these was only 1 who gave a definite reaction to a scratch test (1 plus to ragweed). Sixteen gave entirely negative reactions to the tests, while 3 gave questionable reactions, i. e., a slight erythema which could not be regarded as an unequivocal positive response.

Of the group of 10 patients from whom no history could be obtained there was 1 who gave several positive reactions to scratch tests.

EXPERIMENT 2.—During the course of this investigation an attempt was made to perform the Prausnitz-Küstner (passive transfer) experiment with the spinal

Allergens Employed in Skin Testing

A. Inhalants and Miscellaneous Substances

Bluegrass	Dust	Pyrethrum
Camel hair	Giant ragweed	Rabbit hair
Cat hair	Glue	Redtop
Cattle hair	Goat hair	Rose
Chicken feather	Goldenrod	Rye
Cocklebur	Goose feather	Sheep wool
Corn	Horse dander	Short ragweed
Cotton	Horse serum	Silk
Cottonseed	Kapok	Sumac
Dahlia	Marsh elder	Trichophyton
Dandelion	Orchard grass	Timothy
Dog hair	Orris	Tobacco
Duck feather	Plantain	

B. Foods

Almond	Cocoa	Mackerel	Potato
Apple	Codfish	Milk	Sweet potato
Asparagus	Coffee	Mustard	Prune
Banana	Corn	Oat	Rhubarb
Barley	Crab	Onion	Rice
Bean	Duck meat	Orange	Rye
Beef	Egg white	Oyster	Salmon
Beet	Egg yolk	Paprika	Sole
Bluefish	Garlic	Pea	Spinach
Cabbage	Grape	Peach	Strawberry
Carrot	Grapefruit	Peanut	Tea
Casein	Halibut	Pear	Tomato
Cauliflower	Herring	Pecan	Tuna fish
Celery	Lamb meat	Pepper (black)	Turkey meat
American cheese	Lemon	Pepper (red and green)	Veal
Chestnut	Lettuce	Pineapple	Wheat
Chicken meat	Lima bean	Pork	Whitefish
Clam	Lobster		Flounder

fluid of a patient with multiple sclerosis whose skin had, on scratch testing, given marked wheal reactions to several foods and inhalants and who gave a history of having had hay fever.

The following technic was employed: Sterile cerebrospinal fluid from the patient with multiple sclerosis was obtained by lumbar puncture, and 0.1 cc. of this was injected intracutaneously into several sites on one arm of each of several normal subjects. Sites on the other arm of each of the same normal subjects were prepared as controls by injecting 0.1 cc. of the spinal fluid of a control subject who did not suffer from multiple sclerosis, who had no familial or personal history of atopy and who did not give positive reactions to any of the 64 to 70 foods or 34 inhalants employed in scratch testing. Twenty-four hours later the prepared sites were "scratch tested" with a number of foods and inhalants to which the skin of the patient with multiple sclerosis had reacted.

The results of these passive transfer experiments were essentially negative; i. e., no evidence was found in the spinal fluid of this patient of the presence of antibodies to foods or inhalants similar to the reagins commonly found in the blood serum of patients with hay fever.

However, some weakly positive wheal reactions were obtained with the spinal fluid of the patient with multiple sclerosis when the spinal fluid was freshly taken and injected immediately into the skin of a normal test subject and the sites tested with allergens twenty-four hours later; the sites prepared with the spinal fluids of normal control subjects were always negative.

These reactions suggest that we may have been dealing with weak (labile) antibodies present in the spinal fluid of the patient with multiple sclerosis, demonstrable by passive transfer only when the spinal fluid was injected immediately after it had been obtained through lumbar puncture. One would be able to explain such a phenomenon either by the small amount of antibody present or by a qualitative difference between reagins found in the blood serum and the antibody occurring in the spinal fluid.

The present evidence for the existence of passive transfer antibodies in the spinal fluid is much too meager to permit of any conclusions, although our results seem to warrant further studies in this direction.

COMMENT AND CONCLUSIONS

It is not easy to fix the actual incidence of atopy in the total population, and the interpretation of our results must, of course, depend to a great extent on the comparison of our findings with those in an equivalent normal group.

However, in our own opinion and experience, the incidence of atopic sensitivity found in this group of cases of multiple sclerosis is little higher than that which is to be expected in any equivalent unselected group studied by the same methods.

Of our 30 patients with multiple sclerosis who were completely studied, 10, or 33 per cent, presented evidence of personal or familial atopic disease or positive wheal reactions to skin tests or both. When these figures are compared with those in the literature relating to the incidence of atopy in an unselected population, it will be seen that our results correspond with the high average values submitted by investigators who have performed similar studies on unselected groups.[3]

We conclude therefore that, with the criteria and methods described and with allowance for the factor of error present in a series of this small size, our results in the 40 cases of multiple sclerosis do not demonstrate a significant increase over the normal incidence of atopy.

3. Rackemann, F. M., and Simon, F. A.: Technic on Intracutaneous Tests and Results of Routine Tests in Normal Persons, J. Allergy **6**:184, 1935. Grow, M. H., and Heiman, N. B.: Intracutaneous Tests in Normal Individuals: An Analysis of One Hundred and Fifty Subjects, ibid. **7**:108, 1936.

This statement does not, of course, exclude the possibility that in an occasional instance multiple sclerosis–like symptoms may be caused by an atopic mechanism. Nor do our results in any way preclude the possibility that some nonatopic form of allergy may play a role in multiple sclerosis

It may also be worthy of comment that in our group of patients there was almost complete agreement between the incidence of positive reactions to scratch tests with food and inhalant allergens and a familial or personal history of atopy. This suggests that the skin test as we employed it is a fairly reliable method for the demonstration of atopy.

We were not able to obtain any proof of the presence of Prausnitz-Küstner (passive transfer) antibodies in the spinal fluid of 1 of our patients with multiple sclerosis who was atopic. The patient was the only subject whose spinal fluid was studied in this way. However, the questionable or suggestive reactions obtained when the spinal fluid was injected into the test subject immediately after it had been taken indicate the necessity for further studies in this direction and for more extensive attempts to demonstrate Prausnitz-Küstner reagins in the cerebrospinal fluid of various diseases of the cerebrospinal axis.

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GROSS PATHOLOGY OF THE OLIGODENDROGLIOMAS

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Oligodendrogliomas as a distinct group were first described by Bailey and Cushing,[1] and an accurate description of the histologic features of the tumor has been given by Bailey and Bucy,[2] Környey [3] and other authors. Little attention, however, has been paid to the gross pathologic character of this complicated neoplasm, except in the intraventricular type, which was studied by Bailey and Cushing,[1] Dickson,[4] Greenfield and Robertson,[5] Kwan and Alpers [6] and Thomas and Jumentié.[7] It is the purpose of this paper to demonstrate that this tumor may be classified under several varieties as determined by its distribution and type of growth. From our material the following classification may be made: (1) bilateral type, involving both hemispheres; (2) unilateral type, involving one hemisphere; (3) oligodendroglioma of the ventricles and (4) oligodendroglioma of the basal ganglia. In the literature we have found additional types, with involvement of the brain stem (Agostini [8]), of the cerebellum (Garcavy [9]) and of the spinal cord (Kernohan [10]). We shall be concerned here mainly with the gross pathologic picture, referring to the histologic features only when necessary for interpretation.

From the Neuropsychiatric Institute, R. W. Waggoner, M.D., Director, and the Department of Neuro-Surgery, Max M. Peet, M.D., Chairman, University of Michigan Medical School.

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REPORT OF CASES

BILATERAL OLIGODENDROGLIOMA

CASE 1.—W. C., a white man aged 41, was admitted to the hospital on May 21, 1930, with a history of convulsive attacks, of five months' duration.

Neurologic examination revealed only a questionable Babinski and positive Oppenheim, Gordon and Chaddock signs on the left. An encephalogram showed that the right ventricle was larger than the left, the latter being slightly displaced to the right. The patient left the hospital, but returned two years later with a history that in the interval he had had ten grand mal convulsive attacks accompanied by twitchings of the facial muscles and ringing in the ears. At this time neurologic examination revealed a slight increase in the right knee jerk, a questionable Oppenheim sign on the left, slight weakness of the left hand grip, slight ataxia in the finger to nose test bilaterally and a definite adiadokokinesis on the left.

A second encephalogram demonstrated enlargement of the anterior horn of both ventricles, more on the right. In the brain substance along the margins of both anterior horns there were distinct, irregularly outlined opacities, which could be seen in sagittal and lateral projections, and multiple areas of calcification in both frontal lobes. It was reported that "as compared with the previous encephalogram, abnormal shadows within the brain substance could be clearly visualized, but that the disproportion in size between the ventricles had not changed."

Operation and Course.—On Oct. 4, 1932 an osteoplastic craniotomy was performed, and part of a tumor was excised from the right frontal lobe. The postoperative course was characterized by periods of confusion and frequent convulsive attacks, followed by slow, progressive mental and physical deterioration. Death occurred four years after operation. The approximate duration of the disease was six years.

Postmortem Examination.—The brain weighed 1,425 Gm. The rostral part of the right superior and of the middle frontal gyrus had been removed by the surgeon. In the remaining parts of these gyri there were two nodular tumors, measuring 3 by 2 cm., which were moderately well demarcated, soft in consistency and pinkish gray. The entire corpus callosum was enlarged. From the greatly thickened genu and anterior part of the body of the corpus callosum the tumor extended into the white matter of both frontal lobes; from the posterior part of its body and from the splenium numerous small nodular tumors extended into both parietal lobes, the precuneus, the cuneus and the right pulvinar. In the white matter of both frontal lobes there were large symmetric areas of calcification.

Weigert preparations revealed additional details. In sections through the anterior part of the corpus callosum there were complete demyelination and irregular thickening of the genu and rostrum (fig. 1). At this level the anterior horn of the left ventricle was narrower than that of the right; both were distorted and surrounded by areas of demyelination from 1 to 1.5 cm. in width. On the right the tumor extended into the anterior horn of the ventricle. In both semioval centers the myelin content was greatly reduced, and there were large symmetric areas of calcification. There was diffuse demyelination throughout the white matter of both frontal and parietal lobes, and in the white matter of the right fusiform, inferior temporal and calcarine gyri. In addition, these regions contained numerous, well demarcated foci of a much lighter hue, representing small nodular tumors (fig. 2). This nodular character of the growth was particularly well demonstrated in sections through the midpart of the thalamus (fig. 3). At this level there were a large circumscribed area of demyelination

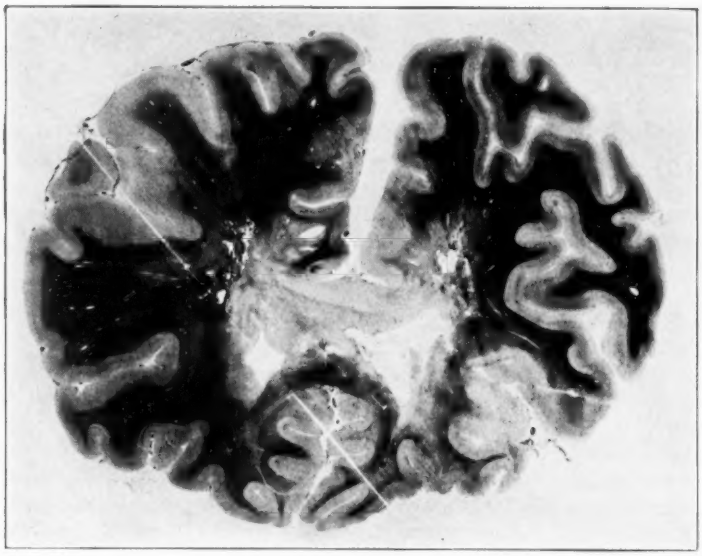

Fig. 1.—Section through the rostral part of the corpus callosum. The latter is completely demyelinated. There are large symmetric areas of calcium deposits in the white matter of the frontal lobes. The anterior horns of the ventricles are asymmetric and are surrounded by an area of demyelinated tissue. Streaks in the section are due to damage to the knife caused by calcified tissue. Weigert stain; reduced to one-half natural size.

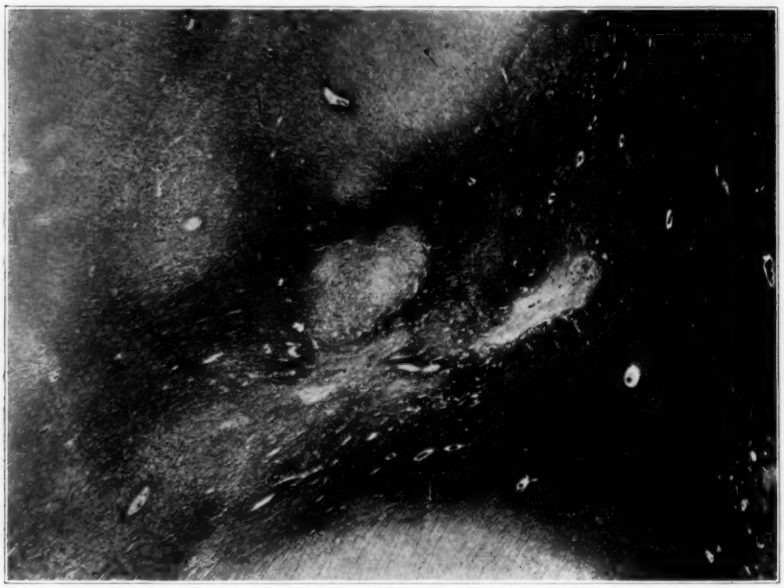

Fig. 2.—Photomicrograph showing small nodular tumors in the white matter of the right temporal lobe. Weigert stain; Zeiss planar lens, 50 mm.

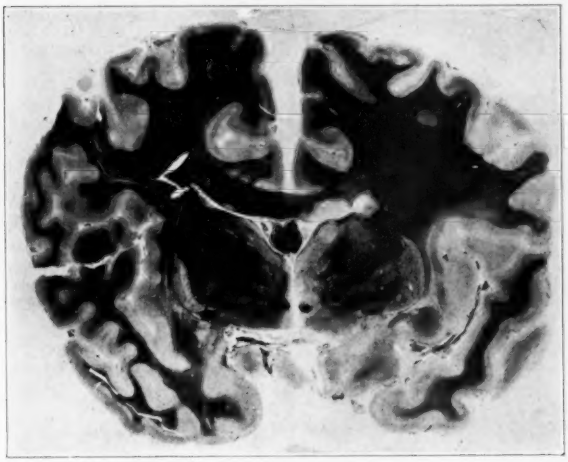

Fig. 3.—Large nodular tumor in the right side of the corpus callosum, small tumors in the left side and the white matter of the left gyrus cinguli. Weigert stain.

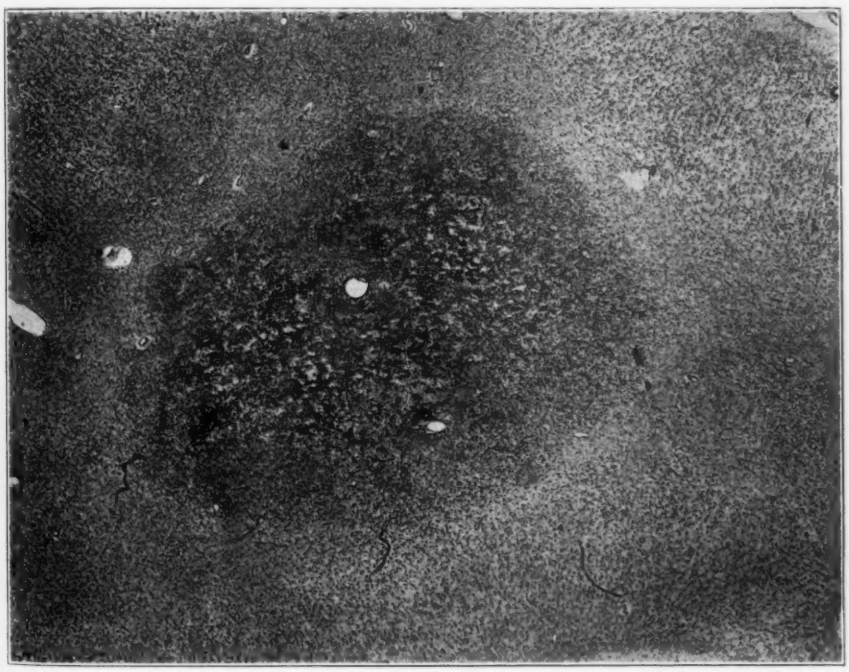

Fig. 4.—Photomicrograph showing a nodular tumor in the white matter of the left frontal lobe. Nissl stain; Zeiss planar lens, 35 mm.

TABLE 1.—*Tabulation of Data in Cases of Bilateral Oligodendroglioma*

Case No., Sex, Age, Yr.	Neurologic Findings	Roentgenologic Findings	Surgical Observations	Duration and Outcome of Disease	Pathoanatomic Examination	Interpretation
1	Described in the text					
2. H. V. M, 28	History of paroxysmal convulsive attacks and blurred vision for 14 mo. Bilateral Hoffmann's sign; astereognosis on right, dysarthria; impaired memory	Multiple areas of calcification in left frontal lobe, extending to midline	Part of large tumor of left frontal lobe removed	Purulent meningitis and death 2 mo. later; duration of disease 16 mo.	Autopsy: tumor of genu of corpus callosum and both frontal lobes	Invasion of both frontal lobes suggested that nucleus of tumor was in genu of corpus callosum
3. M. S. F, 37	History of irritability, severe headaches, twitchings in right leg for 7 mo.; attacks of unconsciousness. Patient euphoric, facetious and retarded; tenderness over both frontal areas, bilateral choked disks of 5 D.	Depression and posterior displacement of both frontal horns, suggesting a lesion involving anterior part of corpus callosum and both frontal lobes	Part of large tumor of right frontal lobe, infiltrating anterior part of corpus callosum and left frontal lobe, removed	Death 40 hr. after operation; duration of disease 7 mo.	Autopsy: tumor in genu of corpus callosum extending symmetrically into centrum semiovale of both sides	Nucleus of tumor was in genu of corpus callosum, from which growth invaded both frontal lobes
4. D. W. M, 38	History of headaches and "fainting spells" for 3½ mo. Right side of face weaker than left; biceps, triceps and knee reflexes absent on right; bilateral edema and choked disks of 6 D.	Irregular area of calcification, measuring 1½ inches, in left frontal lobe, near midline	Partly calcified tumor in anterior part of left frontal lobe removed	Postoperative improvement lasting 30 mo.; sudden death 10/26/34; duration of disease approximately 3 yr.	Autopsy: tumor tissue in anterior part of corpus callosum and both frontal lobes	Nucleus of tumor was in anterior part of corpus callosum, from which it extended into both frontal lobes
5. K. H. F, 43	History of headaches for 2 yr. Patient euphoric, facetious and disoriented; memory impaired; bilateral exophthalmos; veins of eyelids and conjunctivas dilated; disks blurred, definite limitation of lateral rotation of both eyes; hearing moderately reduced on right; moderate ataxia of left arm	Irregular areas of calcification in left frontal lobe; small calcified area in right frontal lobe	Part of large tumor of left frontal lobe removed; growth extended into anterior part of corpus callosum and right frontal lobe	Death 1 hr. after operation: duration of disease approximately 2 yr.	Autopsy: tumor of genu and anterior part of corpus callosum, of both frontal lobes and of left caudate nucleus	Nucleus of tumor was in anterior part of corpus callosum, from which growth invaded both frontal lobes, more on left
6. V. S. F, 54	Patient semicomatose on admission; incoherent; disoriented; bilateral choked disks of 2 D. with hemorrhages; all tendon reflexes hyperactive; sustained ankle clonus on right; bilateral Hoffmann's sign	Area of calcification in right frontal lobe, extending to midline	Part of large calcified tumor removed from right frontal lobe; growth extended into anterior part of corpus callosum and into left frontal lobe	Duration of disease unknown; death 3 wk. after operation	Autopsy: tumor of both frontal lobes, anterior part of corpus callosum and anterior part of septum pellucidum	Nucleus of tumor was in anterior part of corpus callosum, from which it invaded both frontal lobes
7. L. S. M, 50	History of headaches, nausea, vomiting and dizziness for 1 yr. Patient semicomatose; pupils contracted, the right slightly larger; both reacting sluggishly; biceps, triceps and radial reflexes hyperactive; coarse tremor of both arms, muscular twitchings of left arm and leg and of left corner of mouth	Area of calcification, approximately 1 inch in diameter, in anterior part of falx, extending to both sides of midline	Biopsy: tumor invading anterior part of corpus callosum and both frontal lobes. Large part of right frontal lobe, part of genu of corpus callosum and of left frontal lobe removed	Death 20 mo. later, in another hospital; duration of disease approximately 3 yr.; no autopsy	.....	Surgical observations indicate bilateral frontal tumor with nucleus in anterior part of corpus callosum
8. W. L.	History of attacks of unconsciousness for approximately 5 yr. Patient drowsy and disoriented, but no other neurologic symptoms noted	Large area of calcification in left frontal lobe, extending to midline	Biopsy: left frontal craniotomy revealed large gelatinous, partly calcified tumor in anterior part of corpus callosum and in both frontal lobes; large part of left frontal lobe was removed	Patient died 8 mo. after operation	.....	Surgical observations suggest that nucleus of tumor was in anterior part of corpus callosum, from which it invaded both frontal lobes

in the right side of the corpus callosum, a smaller area in the left side and two distinct foci in the white matter of the left gyrus cinguli.

Histologic examination revealed diffuse invasion by the growth of the white and gray matter, with condensation into numerous irregularly scattered nodules, measuring from 1 to 6 mm. in width, which were connected by a continuous stream of tumor elements (fig. 4). These nodular tumors corresponded to the circumscribed areas of demyelination already noted in Weigert sections. From the superficial strata of the gray matter the tumor invaded the leptomeninges of both hemispheres.

Interpretation.—Advanced demyelination in the genu of the corpus callosum suggested that the nucleus of the tumor was in the genu, with secondary invasion of both hemispheres. It had extended into the body of the corpus callosum, and thence to both frontal and both parietal lobes, the base of the right temporal lobe, the right occipital lobe and the right pulvinar. The tumor elements penetrated all structures of the involved areas, with the exception of the perivascular spaces. The invasion of the meninges occurred by continuous growth from the cortex. The outstanding features were large symmetric areas of calcification in the white matter of both frontal lobes, condensation of the growth into numerous nodular tumors, connected by a stream of tumor cells, and invasion of the anterior horn of the right ventricle.

A tabulation of the cases of bilateral tumors is given in table 1.

UNILATERAL OLIGODENDROGLIOMA

CASE 9.—*Solitary tumor of the left frontal lobe.*

Y. J., a white man aged 33, was admitted to the hospital on March 23, 1931, with a history of frontal headaches for two years. Neurologic examination showed sluggish reaction of the pupils to light and blurring of the nasal margins of the disks, but no other pathologic findings. After a lumbar puncture the patient became disoriented and later semistuporous, remaining so for one week. He died on April 30. The approximate duration of the illness was two years.

Postmortem Examination.—There was a tumor in the left frontal lobe which occupied approximately the rostral third of its convexity, the entire base and the rostral half of its median surface. The meninges overlying the median surface of both frontal lobes were infiltrated and fused by tumor tissue. Weigert sections revealed complete demyelination of the rostral half of the left frontal lobe and moderate demyelination of the left centrum semiovale and of the dorsal fibers of the left side of the genu of the corpus callosum (fig. 5). The right hemisphere was free of tumor.

Interpretation.—In this instance the tumor was restricted to the left frontal lobe, showing only limited involvement of the left side of the genu of the corpus callosum. Of interest were the invasion of the meninges of the right frontal lobe and the absence of calcification.

CASE 10.—*Oligodendroglioma in the right posterior parietal lobe, with severe edema of both hemispheres.*

W. W., a white man aged 58, was admitted to the hospital on April 6, 1930, with a history of frontal and occipital headaches, vomiting and attacks of unconsciousness for two years. During the last six weeks there had been periods of mental confusion. On examination the pupils were small and did not react to light; there were slight weakness of the left lateral rectus muscle and papilledema of 2 D. on the right and of 3 D. on the left, with hemorrhages on both sides. There were astereognosis on the left and positive Babinski, Oppenheim and Schaffer signs and abortive ankle clonus on the right. There was loss of sense of position in both feet. There were marked dyssynergia and dysmetria associated

Fig. 5.—Bulky tumor of the left frontal lobe, without tendency to invade the opposite hemisphere. Weigert stain; one-third natural size.

with muscular weakness, on the left side. Speech was clear, but there was a mild memory defect. Ventriculographic examination was attempted, but a large cyst containing xanthochromic fluid was encountered in the right posterior parietal region. The ventricle was not tapped. The patient died twelve hours after the ventriculographic procedure. The approximate duration of the illness was two years.

Postmortem Examination.—In the right posterior parietal region the dura was firmly attached to the leptomeninges and was removed with difficulty, leaving a punched-out defect, measuring 3 by 3 by 1.5 cm. in the brain substance. The bulk of the tumor was in the right parieto-occipital region, in which it occupied the inferior parietal and the lateral occipital gyri (fig. 6 *A*). The growth

extended into the right precentral and middle frontal gyri, invading the gray and the superficial layers of the white matter (fig. 6 *B*). The tumor contained numerous cystic cavities filled with coagulated milky fluid. There was marked edema of both hemispheres, more on the right (fig. 6 *B*). The anterior horn of the right ventricle was dilated; that of the left ventricle was narrow. The

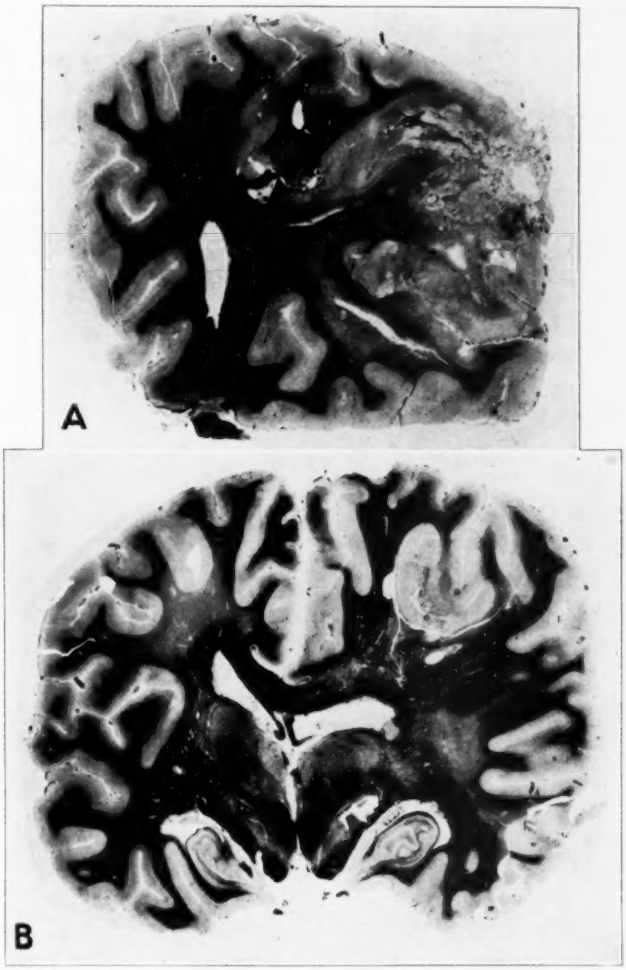

Fig. 6 (case 10).—*A*, an oligodendroglioma of the right parieto-occipital region, involving chiefly the gray matter. Reduced to one-third natural size. *B*, tumor of the right parieto-occipital region, a portion of which is shown in *A*, extending into the cortex and the superficial strata of the white matter of the precentral region, with edema of both hemispheres. Reduced to one-half natural size. Weigert stain.

corpus callosum was not enlarged. Histologic examination disclosed no growth in the left hemisphere. There were small deposits of calcium within the tumor and numerous deposits throughout the gray matter of both hemispheres.

Interpretation.—The nucleus of the tumor apparently was in the right parieto-occipital region, from which it extended frontally, invading the gray matter and the leptomeninges and pachymeninges; however, it did not involve the deep parts of the white matter and the corpus callosum. The tumor therefore remained unilateral, but in spite of this produced severe edema of both hemispheres.

CASE 11.—*Unilateral oligodendroglioma of the right frontal lobe, with metastases in the opposite side.*

T. N., a white man aged 58, was admitted to the hospital on Feb, 23, 1935, with a history of right frontoparietal headaches, dizziness, vomiting and retarded thinking for approximately three months. Six weeks before admission he had had

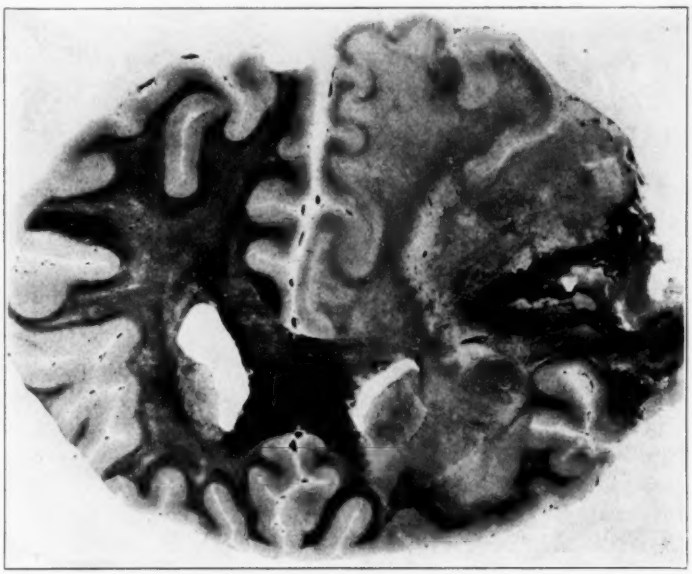

Fig. 7.—Large, partly necrotic oligodendroglioma of the right frontal lobe. The latter is enlarged and demyelinated. Note the areas of demyelination in the corpus callosum and in the left frontal lobe. Weigert stain; reduced to one-half natural size.

"two falling spells" without loss of consciousness, and then had developed weakness of the left arm and leg. Vision became poor. During the last two weeks he had complained of smelling disagreeable odors.

The patient was disoriented for time and place. The left pupil was larger than the right, but both reacted well to light and in accommodation. Vision was blurred, but the eyegrounds were normal. Hearing was diminshed on the right. There was weakness of the left lower part of the face and of the left arm and leg. Babinski, Oppenheim and Chaddock signs were positive on the left. The patient walked with difficulty, tending to fall to the left. Roentgen examination showed slight displacement of the pineal shadow to the left. A right parietal osteoplastic craniotomy was performed, and part of a tumor infiltrating the right frontoparietal region was excised. The patient failed to

improve and died thirty-five days after the operation. The approximate duration of the illness was six months.

Postmortem Examination.—The right hemisphere was larger than the left; there was a tumor in the right frontal lobe, measuring 4 by 4 cm., which was yellowish and partly necrotic and contained numerous hemorrhages (fig. 7). In Weigert preparations the white matter surrounding the tumor in the right frontal lobe stained grayish black and was edematous. The genu of the corpus callosum and the white matter of the entire left frontal lobe were also diffusely demyelinated (fig. 7). Sections through the frontoparietal region disclosed the posterior limit of the tumor to be in the white matter of the right operculum, with several nodular tumors in the dorsal parts of the internal and external capsules (fig. 8).

Fig. 8.—Posterior pole of the tumor and several nodular tumors in the internal and external capsules. Weigert stain; reduced to two-thirds natural size.

Histologic examination revealed unusually extensive invasion of the vascular system of both parietal and both frontal lobes. The growth invaded the perivascular spaces, the thickened vessels appearing in Weigert sections as yellow lines and points. An unbroken chain of these vessels extended through the genu and the rostral part of the body of the corpus callosum, forming in the white matter of the posterior part of the left frontal lobe a metastatic tumor measuring 1 by 0.7 cm. (fig. 9). There was also universal invasion of the leptomeninges.

In this case there was a unilateral oligodendroglioma of the right frontal lobe, with widespread invasion of the perivascular spaces, result-

ing in metastases in the left hemisphere and universal invasion of the meninges. This massive metastatic invasion of the opposite hemisphere differs fundamentally from the bilateral growth which originates in the corpus callosum and invades both hemispheres by direct extension.

Included in table 2 are 7 cases which cannot be classified with certainty under either of the aforementioned groups. One of the patients (case 12) is still living; the outcome in case 18 is not known, and in the rest (cases 13, 14, 15, 16 and 17) autopsies were not performed. Blurred outlines of both anterior horns in case 14 suggested a

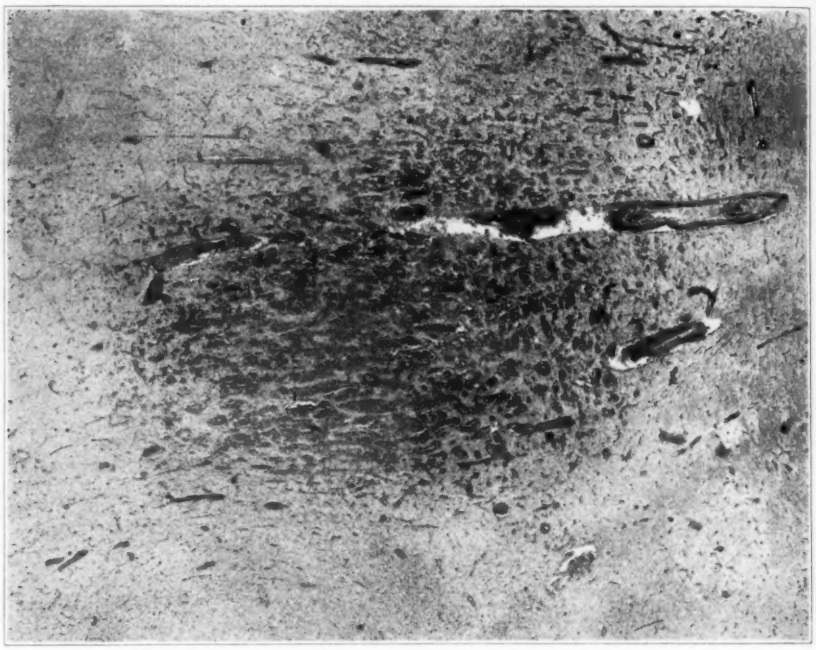

Fig. 9.—Photomicrograph showing a metastatic (perivascular) tumor in the left frontal lobe. Nissl stain; Zeiss planar lens, 20 mm.

bilateral type of growth. Because of the long postoperative survival and paucity of symptoms in cases 12 and 13 it may be assumed that the tumor was unilateral.

INTRAVENTRICULAR OLIGODENDROGLIOMA.

CASE 19.—L. C., a white woman aged 51, was admitted to the hospital on Dec. 21, 1930 in coma. There was a history of "dizzy spells" and convulsive attacks for fourteen years. One year before admission the patient had suddenly collapsed in the street. In the nine months before admission there were frontal headaches, nausea, dizziness, loss of vision and a tendency to sway to the left

TABLE 2.—*Tabulation of Data in Cases of Oligodendroglioma Not Classifiable as Unilateral or Bilateral*

Case No., Sex, Age, Yr.	Neurologic Findings	Roentgenologic Findings	Surgical Observations	Duration and Outcome of Disease	Interpretation
12. E. C. F, 28	History of paroxysmal convulsive attacks and blurred vision for 2 yr.; no other neurologic finding	Calcium deposits in right frontal lobe	Calcified tumor in posterior part of right frontal lobe was partially removed	Patient survived operation 48 mo.; died during convulsive attack	Long postoperative survival suggests unilateral tumor
13. C. M. F, 18	History of convulsive attacks for 2 yr.; nystagmoid movements on lateral deviation of eyes; tendency to walk to right with eyes closed	Calcified area in left parietal lobe	Part of a calcified tumor was removed from left posterior parietal region	Patient living, 60 mo. after operation, but has numerous convulsive attacks	Long postoperative survival suggests unilateral tumor
14. N. C. M, 34	History of headaches and convulsive attacks for 1 yr.; right pupil larger than left; marked nystagmus on looking to right; grip of right hand weak, weakness of right leg; bilateral choked disks of 2 D.	Left ventricle enlarged; outlines of both ventricles blurred	Part of large parasagittal tumor involving right frontal lobe and anterior horn of right ventricle was removed	Death 16 mo. after operation	Blurring of both ventricles suggests bilateral tumor
15. T. S. F, 41	History of headaches and vomiting for 8 mo.; failing eyesight, loss of memory, speech difficulty, unsteady gait, weakness of right side of face; drowsiness, euphoria, unmotivated laughter, partial disorientation; papilledema on right; right pupil larger than left; hearing diminished; bilateral Hoffmann and Babinski signs	Dilation and displacement of both anterior horns	Part of large tumor infiltrating entire left frontal lobe and large parts of parietal and temporal lobes was removed	Patient discharged after operation; no further information available	Extensive lesion of left frontal, parietal and temporal lobes; further interpretation not possible
16. W. B. F, 44	History of headaches, vomiting, dizziness, attacks of unconsciousness, blurred vision and deafness for 14 mo. Patient semicomatose; reaction of pupils sluggish; definite Gordon's sign on left; bilateral papilledema of 1.5 D.	None	Part of cystic tumor of left frontal lobe was removed; tumor was adherent to the dura	Death 2 yr. after operation; duration of disease approximately 4 yr.; no autopsy	Because of lack of data interpretation not possible
17. M. G. F, 28	History of convulsive attacks for 14 mo.; slight nystagmoid movements on rotation of eyes to left	Area of calcification 2 cm. in diameter in left frontoparietal region	First craniotomy 3/31/31; part of a tumor of left posterior frontal region was removed; second operation 7/3/37	Death 3 mo. after second operation; duration of disease 8 yr.; no autopsy	Because of long duration of disease it is probable that tumor was unilateral
18. K. C. F, 46	In 1931 "feeling of numbness" involving left side of body and speech disturbances; in 1937 patient semicomatose, speech unintelligible, motor perseveration marked. Reflexes in both upper extremities increased; marked paresis of left leg; knee and ankle reflexes exaggerated, more so on left; inconstant bilateral Babinski's sign	In 1931 right ventricle not filled with air; third and both lateral ventricles displaced slightly to right; in 1937 large area of calcification in right temporoparietal region; both lateral ventricles distorted	In 1937 right temporoparietal craniotomy was performed; part of a large tumor occupying entire right temporal lobe and extending into frontal and parietal lobes was removed	Known duration of disease 6 yr.; patient discharged 2 wk. after operation; final outcome unknown	Available data are not sufficient for interpretation

when walking. The patient gradually became disoriented and confused. On neurologic examination there were slight ptosis on the left and choking of both disks, with hemorrhages. There were marked wasting and weakness of all extremities, positive ankle clonus on the right and a positive Babinski sign bilaterally. The spinal fluid was xanthochromic and under greatly increased pressure. Death occurred on December 25. The approximate duration of the illness was fourteen years.

Postmortem Examination.—The leptomeninges over both convexities were moderately thickened; the convolutions were flattened. The meninges over the infundibulum, the optic chiasm and the base of the pons and cerebellum were greatly thickened, soft, milky and gelatinous. In coronal sections the genu of the corpus callosum, the columns of the fornix and the anterior part of the septum pellucidum were transformed into a soft, milky, gelatinous tumor mass. The growth also invaded the adjacent part of the body of the corpus callosum and the entire ventricular system and extended through the infundibulum into the

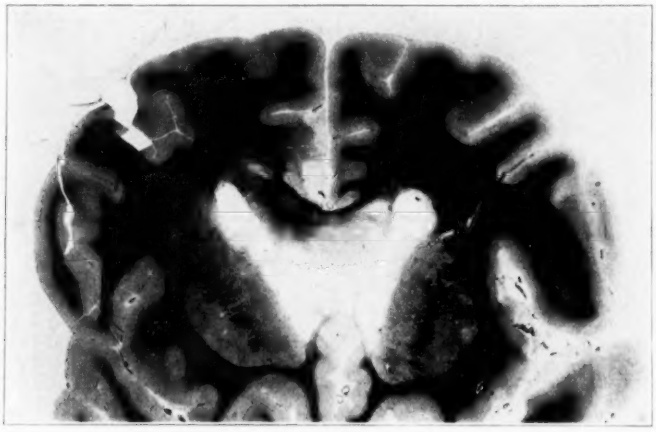

Fig. 10.—The septum pellucidum and the genu of the corpus callosum are replaced by tumor. Note the tumor tissue over both caudate nuclei and in the left gyrus cinguli. Weigert stain; reduced to one-half natural size.

basal meninges (fig. 10). Weigert sections through the rostral part of the corpus callosum disclosed advanced demyelination and thickening of the genu, of the anterior part of the body and of the septum pellucidum. The tumor also invaded the left gyrus cinguli, both parolfactory areas and the right sylvian fissure. The pons, medulla and cerebellum were free of tumor. Histologic examination revealed universal invasion of the leptomeninges.

Interpretation.—The nucleus of the tumor was apparently in the anterior part of the septum pellucidum, although it may have been in the columns of the fornix. The growth involved the septum pellucidum, the genu and the anterior part of the body of the corpus callosum. From the corpus callosum the tumor invaded the gray matter of the left gyrus cinguli, and through the infundibulum it reached the basal meninges, extending into the right sylvian fissure.

CASE 20.—O. N., a white youth aged 17, was admitted to the hospital in 1922 because of feeblemindedness. The brief clinical record stated that the patient had become disinterested and had neglected his personal appearance. He was disoriented for time and place, but was able to answer simple questions. Examination revealed bilateral nystagmus, weakness of the right side of the face and unsteady gait, with dragging of the right foot. Vision grew progressively worse; spastic right hemiplegia developed, and he died six months later. The duration of the disease was unknown.

Postmortem Examination.—The leptomeninges were thin and the convolutions flattened. Coronal sections showed that both lateral ventricles were enlarged, more on the left. They were filled with a soft, grayish-red, gelatinous mass, which occupied the midline, displacing the right lamina of the septum pellucidum to the right, the wings of the fornix ventrally and the corpus callosum dorsally (fig. 11). The tumor did not invade the genu of the corpus callosum, but spread

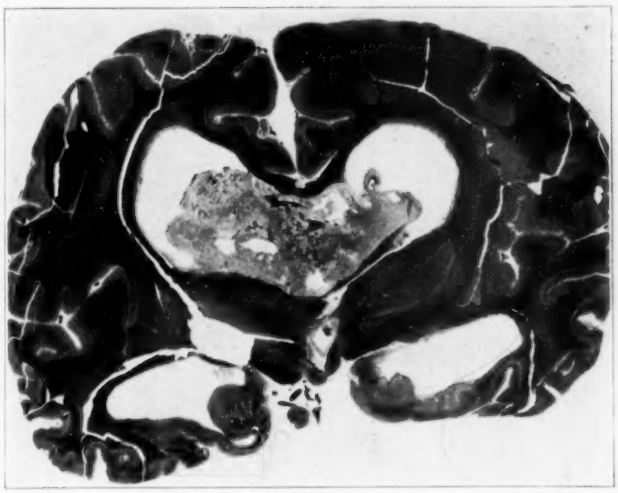

Fig. 11.—Intraventricular oligodendroglioma apparently arising from the left lamina of the septum pellucidum. Weigert stain; reduced to approximately one-half normal size.

beneath its body, filling both anterior and the left posterior horns. Through the foramen of Monro the growth extended into the third ventricle, but the aqueduct and the fourth ventricle remained free.

In Weigert preparations the right lamina of the septum pellucidum could be seen partly covering the tumor, while the left lamina could not be identified. The tumor extended more to the left (fig. 11).

Interpretation.—The location of the tumor between the corpus callosum and the wings of the fornix suggested that the origin of the tumor was in the septum pellucidum, possibly in its left lamina, in view of the relative preservation of the right.

OLIGODENDROGLIOMA OF THE RIGHT THALAMUS

CASE 21.—P. F., a white boy aged 14, was admitted to the hospital on Oct. 30, 1930, with a history of attacks of abdominal pain, nausea and vomiting for eighteen months.

Examination.—The patient was mentally dull and obese and looked older than his stated age. He had gained 67 pounds (30.4 Kg.) during the preceding year. The distribution of hair and fat was of feminine type, and the genitalia were poorly developed. The patient was apathetic and retarded, but was oriented. There were twitching of both eyelids and nystagmoid movements on lateral

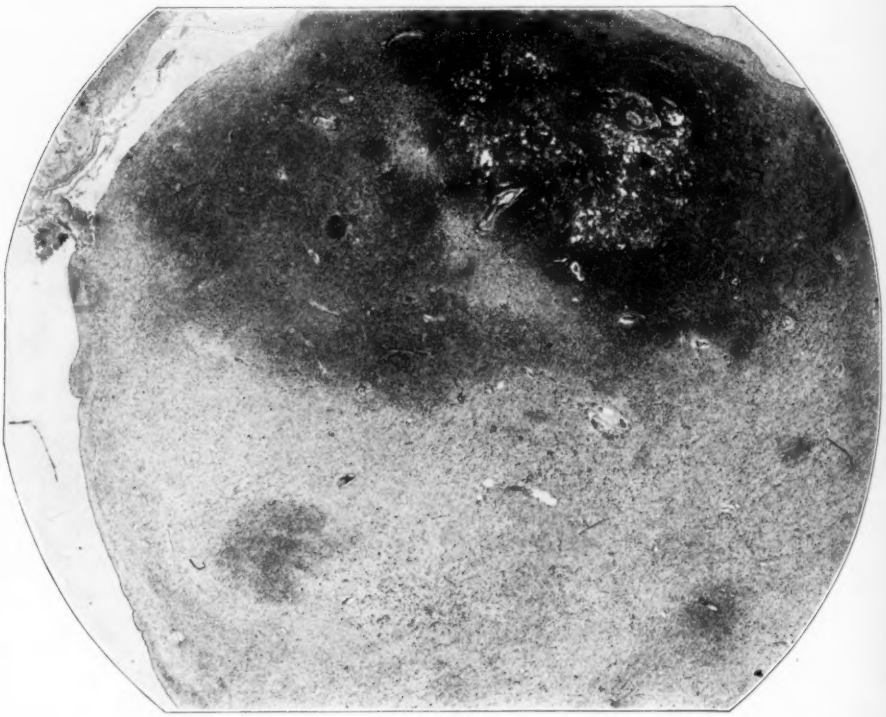

Fig. 12.—Photomicrograph of a partly calcified oligodendroglioma of the right thalamus. Note the numerous small nodular tumors below the large neoplasm. Nissl stain; Zeiss planar lens, 20 mm.

deviation of the eyes; the pupils reacted sluggishly to light. Both fundi were hyperemic, and there was choking of the disks of 2 D. on the right and of 1.5 D. on the left. Contraction of the masseter muscles was weak. There were abortive ankle clonus, a suggestion of Babinski and Oppenheim signs on the left, bilateral ataxia in the heel to knee test and moderate dyssynergia and dysmetria in the finger to nose test. Adiadokokinesis was marked on the left. A dynamometric test gave a reading of 35 on the left and 55 on the right. The basal metabolic rate was —16 per cent.

Roentgen examination revealed rarefaction of the posterior clinoid processes, with relative destruction of the sella turcica and depression of its floor, sug-

gesting a suprasellar tumor and hydrocephalus. Craniotomy was performed on Feb. 13, 1931. No tumor was seen at the base of the brain. After the operation the condition of the patient became progressively worse, and death occurred on February 15. The approximate duration of the illness was two years.

Postmortem Examination.—The convolutions were flattened; the leptomeninges and the basal vessels were thin. Coronal sections showed that the lateral and the third ventricles were greatly enlarged. The septum pellucidum, corpus callosum, fornix and white matter of both hemispheres appeared atrophic. There was bilateral compression of the caudate nucleus, putamen and pallidum and the left thalamus. The right thalamus was enlarged. In the posterior part of the median nucleus and in the anterior part of the pulvinar there was a tumor measuring 1.5 by 1 by 1.5 cm., approximately round, partly calcified and very hard (fig. 12). The enlarged right pulvinar compressed the pineal body, the midbrain and the anterior part of the aqueduct, causing hydrocephalus. The pons, medulla and cerebellum were normal. Histologic examination showed that the tumor invaded diffusely the entire right thalamus and hypothalamus. Scattered through the thalamus there were eight additional nodular tumors, varying in diameter from 1 to 5 mm. (fig. 12). The surrounding formations—caudate nucleus, pallidum and midbrain—were free of tumor, as was the entire ventricular system.

Summary.—This is our only case of oligodendroglioma in the basal ganglia, and we have been unable to find a record of a similar case in the literature. The growth showed several typical features: It was calcified and formed several (eight) small nodular tumors within the invaded area. In spite of proximity to the ventricles, the tumor did not break through the ependyma, but compressed the aqueduct, causing hydrocephalus. The presence of the syndrome of dystrophia adiposogenitalis in association with the tumor may have been due to involvement of the hypothalamus.

COMMENTS

PATHOLOGIC FEATURES

The oligodendroglioma is not a rare tumor. In Bailey and Cushing's series of 412 gliomas, there were 9, or 2.18 per cent; in Környey's 107 gliomas of the hemispheres there were 9, or 8.4 per cent and in our series of 420 gliomas of the hemispheres, basal ganglia, brain stem and cerebellum there were 21, or 5 per cent.

The first classification of this tumor was attempted by Martin,[11] who distinguished two groups: (1) oligodendroglioma of the cerebral hemispheres and (2) oligodendroglioma of the midline (actually the ventricular type). This classification is no longer adequate. On the basis of our material and the reports from the literature, the following classification is offered: (1) bilateral oligodendroglioma of the cerebral hemispheres; (2) unilateral oligodendroglioma of the hemisphere; (3) intraventricular oligodendroglioma; (4) oligodendroglioma of the basal ganglia; (5) oligodendroglioma of the brain stem; (6) oligodendro-

11. Martin, P.: Brain **54**:330, 1931.

glioma of the cerebellum, and (7) oligodendroglioma of the spinal cord. It is possible that the tumor of the optic nerve now called polar spongioblastoma should be regarded as a type of oligodendroglioma (Ostenfeld [12] and others).

We have been able to find in the literature only 1 instance of a bilateral oligodendroglioma involving the cerebral hemispheres. Divrey and Evrard [13] reported a case of invasion of both semioval centers, of the caudate nuclei and of the base of both frontal lobes, but no mention was made of involvement of the corpus callosum. In our series of 21 cases there were 8, or 38.1 per cent, of the bilateral variety. The frequency of this type may even be higher than appears from our figures, since in some of our cases listed in table 2 the condition of the corpus callosum and of the opposite hemisphere is not known; in case 14 blurring of the anterior horns of both ventricles suggests bilateral invasion. In all the cases of bilateral tumor the nucleus of the tumor was in the genu or in the rostral part of the body of the corpus callosum, the invasion roughly following its radiations (cases 1, 2, 3, and 4). In case 1 this was particularly evident; here the genu of the corpus callosum was the only region in which the myelin was entirely destroyed, and could therefore be regarded as the site of the nucleus of the tumor. Extension of the tumor into the body of the corpus callosum may be followed by invasion of the parietal and of the occipital lobes (case 1), and since the growth of the tumor in the body of the corpus callosum apparently proceeds slowly, invasion of the parietal lobes seems to be a later development. We have been unable to find any report in the literature of a bilateral occipital oligodendroglioma with nucleus in the splenium or the posterior part of the corpus callosum. In 1 of Martin's [11] cases a tumor of the occipitoparietal region involved the splenium without affecting the contralateral hemisphere.

Of 21 tumors, 3 definitely were of the unilateral variety (cases 9, 10 and 11). They were located in (1) the left frontal (case 9), (2) the right parieto-occipital region (case 10) and (3) the right fronto-parietal region (case 11). The morphologic character and mode of growth of these unilateral tumors varied greatly. Case 9 represented the least complicated variety, showing a solid, relatively well demarcated tumor which caused moderate edema of the involved right hemisphere and had no tendency to invade the corpus callosum, but invaded the meninges of both frontal lobes. In case 10 the growth invaded large areas of the gray matter of the right parieto-occipital region, but only the superficial strata of the white matter, and caused severe edema of both hemispheres. In case 11 the tumor was a bulky growth invading

12. Ostenfeld, T.: Hospitalstid. **18**:31, 1936.

13. Divrey, P., and Evrard, E.: J. belge de neurol. et de psychiat. **36**:39, 1936.

the gray and the white matter of the right frontoparietal region, causing severe edema of the affected hemisphere. Unusual was the invasion of the perivascular spaces resulting in metastatic involvement of the rostral part of the corpus callosum, of the left frontal lobe and of the leptomeninges. This metastatic involvement of the opposite hemisphere along the perivascular spaces differs fundamentally from the bilateral type of growth which originates in the corpus callosum and invades the hemispheres by direct extension, mainly along the myelin tracts.

In the literature several observations show that oligodendrogliomas in general tend to invade the ventricular system. In Divrey and Evrard's [13] case a bilateral tumor invaded the third ventricle. Bini [14] reported a case of a tumor in the right centrum semiovale extending into the right ventricle. In Martin's [11] second case a tumor of the left parieto-occipital lobe invaded the entire ventricular system, and in the second case of Greenfield and Robertson [5] a frontal tumor invaded both lateral and the third ventricles. In our case 1 the tumor surrounded the anterior horns of both ventricles and broke into their cavity. In case 14 the surgeon noted tumor tissue in the anterior horn of the right ventricle. In all these cases the invasion of the ventricles was secondary, and should not be confused with oligodendrogliomas arising primarily in the ventricles.

Ventricular oligodendrogliomas constitute a definite group. The nucleus of the tumor has been found in different parts of the ventricles. Dickson [4] and Greenfield and Robertson [5] have reported cases in which tumors originated in the floor of the third ventricle and involved the entire ventricular system. In Greenfield and Robertson's [5] case 5 the tumor originated in the fourth ventricle and invaded the aqueduct. Kwan and Alpers [6] reported a case of an oligodendroglioma originating possibly in the mesial wall of the ventricle and filling the anterior horn of the right and the third ventricle. In the case of Thomas and Jumentié [7] the tumor filled the left ventricle, displacing the septum pellucidum to the right and moderately invading the white matter of the left parietal lobe. A tumor which may have arisen from the septum pellucidum was described by Bailey and Cushing.[1] None of these tumors invaded the corpus callosum. In our case 19 it was difficult to determine the exact point of origin of the tumor, but it is likely that it originated in the septum pellucidum or in the columns of the fornix. From there it slowly invaded the ventricular system and the trunk of the corpus callosum, showing little tendency to involve the white matter of the hemispheres, being thus similar to the tumors described by Kwan and Alpers and Thomas and Jumentié. In case 20 the origin of the tumor apparently was in the left lamina of the septum pellucidum.

14. Bini, L.: Policlinico (sez. med.) **43**:445, 1936.

One of the features of oligodendrogliomas is the production of multiple nodular tumors. These focal accretions are not metastatic, since they are interconnected by streams of tumor elements. These nodules varied from 2 cm. in diameter to microscopic size and could be demonstrated best in cases 1, 4 and 21. In case 1 numerous nodules were present in the walls of the anterior horns, causing a deformity demonstrable in a ventriculogram. In case 21 these small tumors were impressive, being crowded into a small area. We could find no similar description in the literature.

From our cases it appears that the oligodendrogliomas have a definite tendency to invade the leptomeninges, and in some cases also the pachymeninges (case 10) and the scalp (Martin [11]).

CLINICAL FEATURES

Of the 8 patients with the bilateral type, the patient in case 1 survived the operation for forty-six months, but the therapeutic result was not satisfactory, since an organic psychosis developed. The best results were obtained in case 4, with relief of symptoms lasting thirty months, and in case 7, with improvement lasting twenty months.

In some of the cases included in table 2 surgical treatment was more successful. One patient (case 13) survived the operation sixty months and is still living. In this case convulsive attacks were the first clinical manifestation; although there was a paucity of neurologic signs, a large area of calcification was seen on roentgenographic examination and made an early diagnosis possible. The patient in case 12 survived the operation forty-eight months, and the patient in case 17, seventy-eight months. In these 3 cases the tumor was possibly unilateral. In none of the cases were the patients entirely free of symptoms after treatment; they continued to have epileptiform attacks. Pathologic examination in the 3 cases of unilateral tumor in which autopsy was performed demonstrated that the neoplasms were too far advanced for surgical treatment. Thus, the prognosis in many of these cases is poor, since symptoms are not usually recognized until an advanced stage is reached.

Five cases of the intraventricular group have been reported in the literature, to which we add 2 cases. Five of these cases occurred in persons in the first three decades of life, and 2 in the sixth. The case of the youngest patient reported by Dickson [4] was that of a child of 6; Greenfield and Robertson's [5] patient was 16 years of age; Bailey and Cushing's [1] patient and the patient in case 20 in our series were 17 years of age, and the patient of Thomas and Jumentié [7] was 23. Finally, in case 5 of Greenfield and Robertson [5] and in our case 19 the patients were 50 years of age.

The most important diagnostic findings are deposits of calcium visible on roentgen examination. These deposits were present in all our cases

of type 1, but were bilateral only in cases 1, 5 and 7. Bilateral calcification in association with deformity of the anterior horns therefore strongly suggests a bilateral frontal oligodendroglioma. In 5 cases of the bilateral group the calcification involved only one hemisphere; unilateral calcium deposits therefore do not exclude a bilateral growth. In 3 cases of unilateral tumors and in the group of intraventricular growths no calcification was noted. In the oligodendroglioma of the thalamus there was a large area of calcification. Of the 7 cases listed in table 2, in which the extent and type of the tumor could not be definitely determined, calcification was present in 4 (cases 12, 13, 17 and 18). The time varies at which sufficient calcium is deposited to make it visible in the roentgenogram. In some instances (cases 12 and 13) calcium was present at an early stage, when neurologic examination still gave normal results, the only symptoms being epileptiform seizures. In others (case 21), in which symptoms strongly suggested a tumor, calcium was not present until several years later; in case 1 there was no calcium at the time of the first examination, while two years later bilateral deposits were seen.

RHYTHMIC VARIATION OF RESPIRATORY EXCURSION WITH BILATERAL INJURY OF CORTICAL EFFERENT FIBERS

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The majority of studies of respiration have been concerned with the respiratory center in the medulla and the factors which influence its activity. Little attention has been given to the control of higher centers over this lower reflex mechanism. Recently, we recorded tremulousness of respiratory movement in cases of palatal myoclonus (Langworthy and Grimmer [1]). In this syndrome there is degeneration of the central tegmental fasciculus, the inferior olivary nucleus and often the dentate nucleus of the cerebellum.

In studying patients at the Baltimore City Hospitals we noticed that many with injury of the motor cortex on one or both sides showed a rhythmic variation of respiratory excursions. This was similar to Cheyne-Stokes respiration, especially in the more marked cases. These patients were not unconscious, nor did they have manifest circulatory inadequacy. Indeed, the respiratory changes persisted for weeks or months. In this paper we shall consider cases in which there was destruction of motor fibers from both cortices. The respiratory changes were present in all the 12 patients who were studied. Often periodicity was not evident on physical examination, but became apparent in the records. It appeared to be due to anatomic changes in the brain which resulted in impairment or loss of the cerebral control over respiration.

Other abnormalities of respiration dependent on unilateral injury of the corticoefferent paths have been described by Kolb and Kleyntjens [2]

From the Subdepartment of Neurology, the Johns Hopkins University, and the Medical Division of the Baltimore City Hospitals.

1. Langworthy, O. R., and Grimmer, R. V.: A Physiological Study of Abnormal Movements Observed in Palatal Myoclonus, with Particular Attention to the Respiratory Rhythm, Bull. Johns Hopkins Hosp. **65**:101, 1939.

2. Kolb, L. C., and Kleyntjens, F.: A Clinical Study of Respiratory Movements in Hemiplegia, Brain **60**:259, 1937.

in cases of hemiplegia. The patients exhibited differences in the expansion of the normal and the abnormal side of the chest, not only in quiet respiration but also in voluntary hyperventilation and in response to carbon dioxide.

Persons with bilateral involvement of the motor fibers from the cortex to the bulbar and spinal nuclei present a typical group of symptoms which form the syndrome of pseudobulbar palsy (Langworthy and Hesser [2a]). In addition to paresis of the extremities, they have difficulties in speaking and swallowing and loss of emotional control, giving rise to forced laughing and crying. The jaw jerk is hyperactive. This syndrome serves as an indication that the control from both cerebral cortices over the cranial nuclei has been impaired. However, the severity of the symptoms shows great variation in different patients; seldom are all the manifestations present in marked form. The respiratory abnormalities are, in general, most pronounced in cases in which the symptoms are most severe. The cerebral damage usually results from vascular disease due to arteriosclerosis, hypertension or syphilis. We studied 1 patient with Friedreich's ataxia who showed the syndrome of pseudobulbar palsy.

There are various causes of periodic breathing; it is difficult to be sure how closely these are interrelated. Cerebral ischemia and anoxemia due to local or general circulatory abnormality probably represent the most common etiologic factor. Toxic conditions, such as uremia, form another group. Rhythmic breathing associated with increased intracranial pressure may be due to cerebral ischemia, as well as to actual anatomic interference with the respiratory mechanism. Normally, periodic breathing is observed in any circumstances in which alveolar carbon dioxide or oxygen tension is reduced abruptly below the normal level. Hence, it follows apnea after voluntary hyperventilation. Likewise, voluntary apnea in the presence of oxygen inadequacy, as seen at high altitudes, may produce periodic breathing. It does not occur when oxygen tension is high. Finally, we shall show that it may follow purely anatomic changes in the brain.

Periodic breathing may take many forms. Depth and rate of respiration may be fixed or changing. Tidal air may encroach on the supplemental or complemental air, producing changes in the base line of the pneumogram. Apnea may or may not be present. There is variation in the duration of the periods as well as the constancy of the periodicity.

2a. Langworthy, O. R., and Hesser, F. H.: Syndrome of Pseudobulbar Palsy: An Anatomic and Physiologic Analysis, Arch. Int. Med., to be published.

METHODS

The respirations are recorded by means of the apparatus shown in the diagram. The balloon of a sphygmomanometer cuff is placed over the epigastrium and is held in position by means of an abdominal binder. This balloon is connected by tubing with a thin rubber balloon, enclosed in a 1 liter glass container. The latter communicates with a tambour, which records on a kymograph.

The balloon on the epigastrium is inflated with air. Movements of the thoracic wall and epigastrium coincident with respiration produce synchronous changes in pressure within this system, so that the balloon in the glass container is ordinarily largest at the end of inspiration and smallest at the end of expiration. The sealed atmospheric pressure in the glass container is influenced by the size of the balloon, and in turn produces changes of pressure in the tambour. This apparatus creates a record in which the upstroke represents inspiration and the downstroke expiration.

In some cases, as is figure *2, 13,* there is forced expiration, in which the abdominal muscles contract strongly. Then the pressure in the epigastric balloon will be increased and an accessory upstroke recorded during expiration.

The amplitude of the recordings can be varied by increasing or decreasing the air pressure in the balloon system.

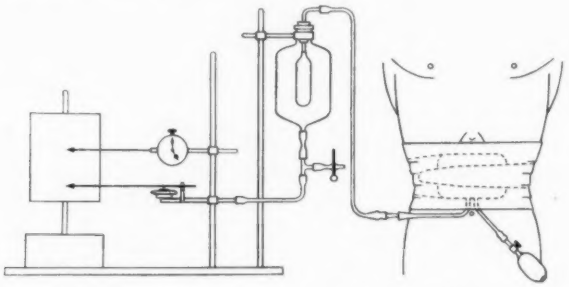

Fig. 1.—Diagram of the apparatus used in recording respirations.

REPORT OF CASES

Records are presented in 3 cases.

CASE 1.—G. W., a white man aged 55, was admitted to the Baltimore City Hospitals with the complaint of progressive weakness, incontinence and personality changes, of two months' duration.

Physical Examination.—The patient presented a masklike expression; sagging jaw; drooling; slurring, dysarthric speech, and easily induced weeping. There were moderate peripheral arteriosclerosis and cardiac enlargement, but no sign of cardiac failure. The blood pressure was 200 systolic and 108 diastolic. There was incontinence of urine and feces. The pupils were small and equal and reacted sluggishly to light. Ophthalmoscopic examination revealed mild arteriosclerotic changes, with slight swelling of the optic disks. There was a brisk jaw jerk. Voluntary facial movements were weak, especially on the left. The patient swallowed with difficulty. The gag reflex was diminished. The voice was monotonous and weak. Protrusion of the tongue was hesitant and limited. There were weakness and spasticity of both arms and legs. All the extremities were held in semiflexion. Voluntary movement of a limited, clumsy sort was present in all

the muscular groups. The patient could not stand. Sensory examination gave unsatisfactory results. Painful stimuli caused outbursts of weeping. The tendon responses were everywhere more active than normal. There were Hoffmann,

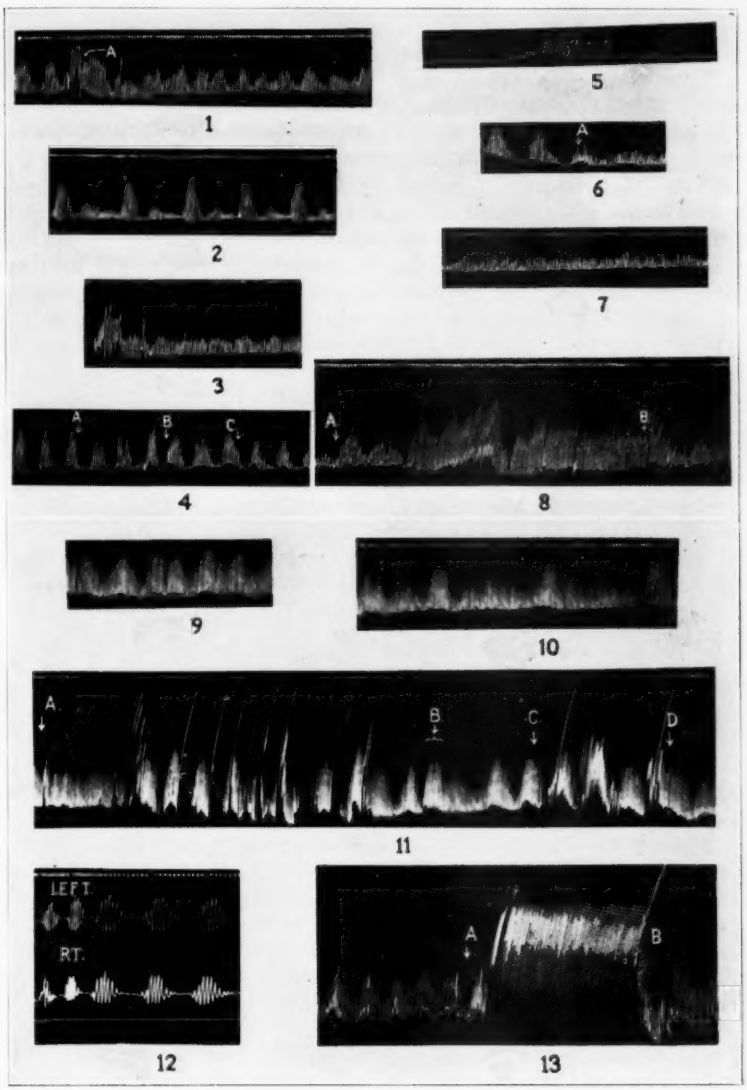

Fig. 2.—Tracings of respirations in 3 cases of bilateral injury to the cortical efferent fibers.

Babinski and Chaddock signs bilaterally. The abdominal and cremasteric reflexes were absent. No clonus could be elicited.

Laboratory tests of the blood gave normal results; the nonprotein nitrogen was 43 mg. per hundred cubic centimeters. The Wassermann reactions of the blood and the spinal fluid were negative. The urine contained a trace of albumin. The

cerebrospinal fluid showed a pressure of 160 mm. of water; the Pandy reaction was positive, and there were 10 cells per cubic millimeter.

Diagnosis.—The diagnosis was hypertensive cardiovascular disease, with cardiac enlargement, cerebral arteriosclerosis and multiple cerebral thromboses, quadriparesis and pseudobulbar palsy.

Respiratory Tracings.—The records illustrated in figure 2, *1* through *8*, inclusive, and *12* were all taken from this patient. The time tracings at the top of the records mark five second intervals. Tracings *1*, *2* and *3* demonstrate the effect of 1.5 cc. of coramine (a 25 per cent solution of pyridine betacarbonic acid diethylamide) in 20 cc. of physiologic solution of sodium chloride, given intravenously. Tracing *1* shows two Cheyne-Stokes respiratory curves at the beginning of the experiment. The intravenous administration of coramine was then started. There was some stimulation of respiration, owing to the pain produced by inserting the needle at *A*. The medication was given slowly over a period of nine minutes. Even before the injection was completed there was improvement in regularity of respiratory excursions, though a definite periodicity was still present.

The record in *2* was started twenty-five minutes after the beginning of injection of coramine. Alternation of large and small waves of respiratory excursion is observed. A similar record (tracing *10*) was obtained from another patient while receiving oxygen.

Tracing *3* was begun forty minutes after the injection of coramine was started. The respiratory excursions were considerably more regular.

Tracing *4* represents a series of rhythmic respiratory variations. At first the patient was awake; at *A* he fell asleep; at *B* he reawakened, and at *C* the catheter to be used for administration of oxygen and carbon dioxide was inserted into the mouth, though no gas was given. The characteristic curves were not appreciably altered by any of these maneuvers, and we conclude that alterations of rhythm following administration of oxygen or carbon dioxide are due entirely to the gas. The minute pulsations between the large waves were caused by the abdominal aorta. The places on the record where these small waves are seen alone represent periods of apnea.

Tracing *5* shows a group of respirations similar to those in tracing *4*, recorded on a drum rotating at a higher speed. Pulsations of the abdominal aorta are seen before and after the respirations and also are superimposed on the curve of each respiration.

In tracing *6* there are, at the left, two characteristic rhythmic waves. Administration of oxygen by oral catheter was started at *A*. The amplitude of the respiratory excursions almost at once became more even.

Tracing *7* shows a portion of the record taken while the patient was receiving oxygen. Although a suggestion of the characteristic waves could be seen, the rhythm was not marked. There were no periods of apnea, and the average depth of respiration was about one-half to one-third that of the deepest respirations before the beginning of administration of oxygen.

Tracing *8* shows the effect of carbon dioxide, which was given through a catheter, as was the oxygen. Carbon dioxide was administered between the points *A* and *B* on the record. The respiratory rhythm soon lost its characteristic pattern, and respirations became deeper almost at once. The respiratory rate was not markedly affected. After the gas had been administered for about six minutes the depth of respirations became fairly constant. Almost immediately after withdrawal of carbon dioxide, respirations became shallower and more irregular in depth. Several minutes were required before the characteristic rhythm recurred.

In order to obtain information concerning the relative respiratory excursion of the two sides of the chest, their movements were recorded separately, but simul-

taneously (tracing *12*). This was done by fastening a balloon to the lower portion of each side of the chest, in the anterior axillary line (Kolb and Kleyntjens [2]). A double recording system was used, and the pressures in the two systems were made equal. There was essentially no difference in the expansion of the two sides of the chest.

CASE 2.—I. C., a Negro man aged 52, was found to have syphilis, hypertensive cardiovascular disease and signs of left hemiplegia when first admitted to the infirmary. Several days later there occurred a generalized convulsion, followed by loss of speech, difficulty in swallowing and weakness of the right side of the body. At the time of examination speech was unintelligible, but the ability to swallow had returned; he was apt to choke while eating. There was weakness of all the extremities.

Examination.—The patient was uncooperative and disoriented. At times he was restless and combative, but there were no outbursts of laughing or crying. The pupils were unequal in size and reacted poorly to light. There was limitation of movement of the eyes. The jaw jerk was overactive. Voluntary movements of the facial muscles were extremely weak. The patient was unable to speak and could only grunt in answer to questions. The tongue was protruded with difficulty and deviated to the right. Muscular tone was increased in the extremities. There was little power of voluntary movement of the arms and legs. The deep reflexes were overactive, and there were Hoffmann and Babinski signs bilaterally. Sensory examination gave unsatisfactory results. The Wassermann reaction of the blood was positive, but that of the spinal fluid was negative. The nonprotein nitrogen content of the blood was 46 mg. per hundred cubic centimeters. The cerebrospinal fluid pressure was 125 mm. of water, with normal dynamics and constituency.

Diagnosis.—The diagnosis was bilateral cerebral thromboses, with double hemiplegia, aphasia and pseudobulbar palsy, due to arteriosclerosis, hypertension and syphilis.

Respiratory Tracings.—Tracings *9*, *10* and *11* were taken from this patient. Record *9* was made while the patient was lying quietly in bed. While the respiratory excursions were seen to vary rhythmically, there were no periods of apnea. The volume of the shallowest respirations was about one-third to one-fourth that of the deepest.

Tracing *10* was made while the patient was receiving oxygen through a catheter. There were periods of large excursions alternating with periods of much smaller ones, as in tracing *2*. The oxygen did not make the excursions equal, although the rhythmic variation was less striking.

At the onset of the graph seen in *11*, the patient was receiving oxygen; this was stopped at *A*. About two minutes later the respirations became more irregular in excursion; marked rhythmic variations appeared again, and these were separated by short periods of apnea. There were frequent deep sighs during the next seven minutes. A similar group of irregular respirations appeared later, between *C* and *D*, while carbon dioxide was administered. Shortly after administration of carbon dioxide was stopped at *D*, the typical respiratory rhythm again appeared. At *B* the patient was asked to take several deep breaths. He tried to cooperate, but was unable to increase the excursion of a single inspiration over that seen during quiet respiration (tracing *9*). These voluntary deep breaths were of less than half the amplitude of the involuntary sighs present after the oxygen was stopped and were also less than those during the administration of carbon dioxide.

CASE 3.—A. W., a Negress aged 54, complained of numerous attacks of weakness and dizziness. Following one of the first of these there was permanent loss

of function in the right arm and leg, associated with difficulty in speaking. Later she became almost completely paralyzed.

Examination.—The patient was obese and showed little spontaneous activity. Speech was slow and dysarthric. The pupils were small and irregular, and reacted poorly to light. She moved the eyes only to a slight degree. Voluntary movements of the facial muscles were limited. There were strong movements of the face on emotional stimulation. Laughing or crying could be induced easily. Swallowing was somewhat difficult. There was limited movement of the tongue on voluntary effort. Weakness and spasticity were marked in all the extremities. There were Hoffmann and Babinski signs bilaterally. The Wassermann reactions of the blood and cerebrospinal fluid were positive. The cerebrospinal fluid showed a pressure of 115 mm. of water, with normal dynamics, and the Pandy reaction was positive. The nonprotein nitrogen of the blood was 35 mg. per hundred cubic centimeters. The blood pressure was 160 systolic and 110 diastolic.

Diagnosis.—The diagnosis was multiple cerebral thromboses, double hemiparesis and pseudobulbar palsy, due to syphilitic vascular disease.

Respiratory Tracings.—The typical respiratory curve taken while the patient was lying quietly in bed is seen at the beginning of record *13*. Near the end of each expiration can be seen smaller waves. These were caused by forced expiration.[3] During the administration of carbon dioxide, started at *A*, forced expirations became marked, so that the graphic excursions of expiration were higher than those of inspiration. The amplitude of the inspiratory tracings gradually decreased during the administration of carbon dioxide, but that of the expiratory excursions remained the same. As soon as the administration of carbon dioxide was stopped at *B*, the respirations resumed a form similar to that at the start of the record. This patient showed no appreciable change in the rhythmic variation of respiratory excursions with administration of oxygen.

COMMENT

There is proof that the cerebral cortex exerts an influence over respiration. Thus, it is possible to affect voluntarily the rate and depth of the respiratory excursions or to hold the breath for a limited period. The thoracic cage is fixed in inspiration, for example, in

3. By forced expiration is meant any part of the expiratory phase that requires active participation of the musculature of the abdominal wall. Intra-abdominal pressure is passively increased in inspiration and actively increased in forced expiration. Thus, the pressure built up passively against the normal recoil of the abdominal muscles is utilized in quiet expiration as soon as the diaphragm relaxes. In the presence of a large abdominal panniculus, the amplitude of quiet inspiration is reduced, because the limit of intra-abdominal pressure against which the diaphragm must act is reached sooner. The required volume of tidal air is made up by forced expiration, after which the initial part of the subsequent quiet inspiration is effected by the downward pull of the panniculus and the abdominal parietes. At the same time this constant force tends to keep the diaphragm pulled down, reduces the supplemental air and may lead eventually to a state of emphysema. These movements are recorded faithfully in the pneumographic tracing. Hence, the pneumogram permits analysis of the sequence of activity of the respiratory muscles; it is inadequate in recording respiratory activity volumetrically. The spirometer records volumetrically, but inevitably interferes with gaseous exchange and does not allow interpretation of muscular activity.

attempting to lift heavy weights. Bucy and Case [4] and Smith [5] have shown that it is possible either to inhibit or to induce respiratory movements on stimulation of definite areas in the cerebral cortices of mammals.

The most important analysis of the control of respiration by the cerebral cortex was made by Hughlings Jackson in 1895.[6] His ideas will be considered in detail. The respiratory center in the medulla represents a low level of integration. It is really made up of two halves, since it has bilateral representation. It controls the motor neurons which innervate directly the muscles of the respiratory cage, that is, the muscles of the larynx, diaphragm and thoracic wall. This medullary center is under the influence of higher levels of integration in the brain. It receives afferent stimuli particularly through the glossopharyngeal and vagus nerves, and is also responsive to chemical changes in the blood. Jackson expressed the belief that the voluntary influences from the cortex act directly on the motor cells supplying the laryngeal, phrenic and costal muscles. Strong voluntary inspiration produces thoracic movements differing from those of normal breathing. Quiet, involuntary respiration is predominantly diaphragmatic; on strong voluntary inspiration the chief motion is costal.

It must be assumed that during voluntary forced inspiration the respiratory center is inhibited by the cerebral cortex, so that the muscles may respond to direct cortical stimuli. When the blood-borne stimuli become excessive, the respiratory center is so strongly stimulated that it regains its sway over the subordinate centers in spite of the cerebral inhibition. Thus, there are two sets of fibers engaged in the voluntary duties of the thoracic cage, motor fibers from the cortex to the lower motor neurons and inhibitory fibers from the cortex to the respiratory center.

In addition to the occasional inhibition of the respiratory center during voluntary movements of the thoracic cage, there is evidence of continuous, but varying, inhibition of the respiratory center by the cortex as it serves in the work of respiration proper. Evidence of the loss of this inhibition is observed in patients with hemiplegia.

Muscles of the body, such as the respiratory muscles, which act in unison on both sides are innervated from both cerebral cortices. In a case of hemiplegia, Jackson expressed the opinion that there was a slightly greater amplitude of quiet respiration on the hemiplegic side,

4. Bucy, P. C., and Case, T. J.: Cortical Innervation of Respiratory Movements, J. Nerv. & Ment. Dis. **84**:156, 1936.

5. Smith, W. K.: The Representation of Respiratory Movements in the Cerebral Cortex, J. Neurophysiol. **1**:55, 1938.

6. Jackson, J. H.: Neurological Abstracts: XV. Superior and Subordinate Centres of the Lowest Level, Lancet **1**:476, 1895.

owing to the loss of inhibition from the opposite cerebral cortex on the respiratory center of the same side. With voluntary breathing, however, there was a slight diminution of movement on the hemiplegic side, due to the loss of motor control from the opposite half of the brain.

The question of abnormalities in movement of the chest in hemiplegic patients has been studied by Kolb and Kleyntjens. They utilized a recording apparatus which demonstrated changes not evident on clinical examination. During the initial period of shock movements are decreased in amplitude on the paralyzed side. Later the size of the respiratory excursions is dependent on the presence or absence of increased tone on the hemiplegic side. If marked spasticity develops the movements are reduced. On the other hand, their amplitude in cases of flaccid hemiplegia is greater on the paralyzed than on the normal side. One may consider hypertonus as an accessory factor decreasing the respiratory excursion. The increased excursion of the paralyzed side of the chest in patients with flaccid paralysis agrees with the theory that the respiratory center has been released from part of the inhibitory control of the cerebral cortex. Moreover, Kolb and Kleyntjens showed that the movements of the paralyzed side of the chest are increased out of proportion to those of the normal side by the inhalation of carbon dioxide.

Jackson also observed that Cheyne-Stokes respiration occurs when the inhibitory control from the cortex of both hemispheres has been removed. He expressed the belief that the respiratory centers are left under the influence of their inherent automatism to a greater degree than usual and are presumably more susceptible to the chemical composition of the blood. The bilateral medullary respiratory centers are still influenced by afferent stimuli through the vagus nerves. Inhibition is eliminated from both sides, whereon respiratory movements become greater, later apnea occurs and the respiratory movements cease. At length the blood-borne stimuli become excessive; the centers are stimulated more strongly, and there follow a number of respiratory movements of gradually increasing amplitude. The blood then being aerated, the respirations diminish gradually in number and amplitude, and there is again a pause.

The majority of authors writing on periodic breathing have agreed with McLeod and Meakins, who stated that it is a sign of severe anoxemia of the central nervous system. This correlates with the fact that increased oxygen tension tends to abolish it.

We have shown, in some of our observations on patients with pseudobulbar palsy, that rhythmicity of respiratory volume can be minimized, sometimes nearly obliterated, by chemical changes in the blood. Thus, theophylline with ethylene diamine and coramine, given intravenously,

each caused the respirations of 1 patient to become much more regular in volume. Oxygen or carbon dioxide administered by oral catheter caused the respiratory volume to become somewhat more regular in several cases, though their effect was not always observable and, when present, was usually less marked than that of coramine or theophylline with ethylene diamine.

We have tried the effect of oxygen and theophylline with ethylene diamine in cases of nonneurologic conditions representing the periodic respiration of cerebral ischemia (cardiac insufficiency and subarachnoid hemorrhage) and found a similar tendency to abolition of the periodicity. Certainly, the action of the chemicals in both the neurologic and the nonneurologic conditions must be similar.

We have not considered the effect of posture in influencing periodic breathing. Changes in posture start periodicity of respiration, probably because of anatomic hindrance to proper aeration of the lungs and resultant cerebral anoxemia. Patients with orthopnea will show Cheyne-Stokes respirations only when lying flat. In 1 of our cases, periodicity was almost abolished when the patient was placed on his side, to reappear when he turned on his back. However, none of our patients was orthopneic. The possible factor of actual weakness or increased tone in the respiratory muscles themselves has not been investigated as a cause of embarrassment to proper aeration.

SUMMARY

Many patients with a bilateral destruction of the cortical efferent fibers show a rhythmic variation of respiratory excursion that is similar to Cheyne-Stokes respiration, especially in the more marked cases. These persons are not unconscious, nor do they have manifest circulatory inadequacy. They show paresis of the extremities, decreased ability to expand the chest voluntarily, difficulties in speaking and swallowing and emotional instability. The rhythm tends to disappear after injection of cardiovascular stimulants, such as coramine or theophylline with ethylene diamine, or on breathing oxygen or carbon dioxide. These substances have a similar effect on Cheyne-Stokes respiration accompanying circulatory inadequacy. Our cases are compared with cases of nonneurologic conditions in which rhythmicity of respiratory excursion is shown. The general mechanism of periodic breathing is considered and the method of cerebral control of respiration discussed.

THE HUMAN PYRAMIDAL TRACT

A FIBER AND NUMERICAL ANALYSIS

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Because of the lack of agreement existing in respect to the origin of the pyramidal tract, it was thought that the application of a refined silver stain to the lower part of the human pyramid might give a clue as to its cells of origin and, in addition, furnish information about the size and number of its component fibers.

It is commonly taught that the fibers of the pyramidal tract originate from the gigantopyramidalis cells of Betz in the motor area (area 4). As these cells are the largest found in the cerebral cortex, it is logical to assume that they give rise to reasonably large fibers. These cells, although conspicuous by their size, are not abundant numerically. On the basis of counts made by Campbell,[1] there are about 25,000 Betz cells on one side of the human cerebral cortex. In contrast to this, Weil and Lassek,[2] using the Bielschowsky technic, calculated that there were ten times as many pyramidal tract fibers, or 250,000, entering the spinal cord at the level of the first cervical segment. This suggests that other than Betz cells may give origin to these motor fibers. Häggqvist[3] studied the size of the pyramidal tract fibers in the monkey, and his work indicates also that they may arise from another source. He found that when the leg portion of the motor area of the monkey was extirpated the large fibers of the pyramidal tract disappeared after sufficient time was allowed for degeneration. When the arm region was ablated the fibers of intermediate diameter were lost, and when the face area was removed fibers of still smaller caliber were absent. From his investigation he concluded that

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1. Campbell, A. W.: Histological Studies on the Localisation of Cerebral Function, Cambridge, University Press, 1905.

2. Weil, A., and Lassek, A. M.: The Quantitative Distribution of the Pyramidal Tract in Man, Arch. Neurol. & Psychiat. **22**:495-510 (Sept.) 1929.

3. Häggqvist, G.: Analysis of Fibers of the Pyramidal Tract, Acta psychiat. et neurol. **12**:457-466, 1937.

the motor area of the monkey contributed fibers of diameters only between 3 and 21 microns. He computed that five sixths of the pyramidal tract fibers were less than 3 microns in diameter. These extremely small fibers, he concluded, had their origin in a region or regions outside area 4. No mention was made of his staining technic except that the medulla was fixed in formaldehyde, and it is surmised that a myelin sheath stain was utilized.

The results of other experimental investigation which has been made on the origin of the pyramidal tract of primates are not in harmony. Kennard [4] described corticospinal fibers arising from the premotor area (area 6 of Brodmann) of the monkey on the basis of Marchi degeneration following ablation. Levin,[5] however, studied retrograde degeneration in the monkey following hemisection of the cord and stated that 20 per cent of the pyramidal tract fibers arise from areas 3, 1, 2 and 5, while the remaining 80 per cent come from area 4.

A vast amount of physiologic investigative work has been done on the pyramidal system without taking into consideration the nature of its component fibers. Ranson [6] showed with his pyridine-silver stain that the corticospinal tract in the rat contains a large number of unmyelinated fibers. McKibben and Wheelis [7] likewise showed in the cat that unmyelinated fibers form a considerable part of the pyramidal projection. The method most widely used in studying the pyramidal tract has been the Marchi stain; yet its efficiency depends wholly on the presence of myelinated fibers, preferably those of large caliber. If the pyramidal tract of all mammals should prove to be a tract comprised mainly of small fibers, many of which are unmyelinated, the Marchi stain would not give its best results with this projection system.

MATERIAL AND METHODS

When Davenport [8] reported that he was obtaining ratios of approximately 1:1 in comparing the number of dorsal root fibers with that of ganglion cells, it was

4. Kennard, M. A.: Corticospinal Fibers Arising in the Premotor Area of the Monkey as Demonstrated by the Marchi Method, Arch. Neurol. & Psychiat. **33**:698-711 (April) 1935.

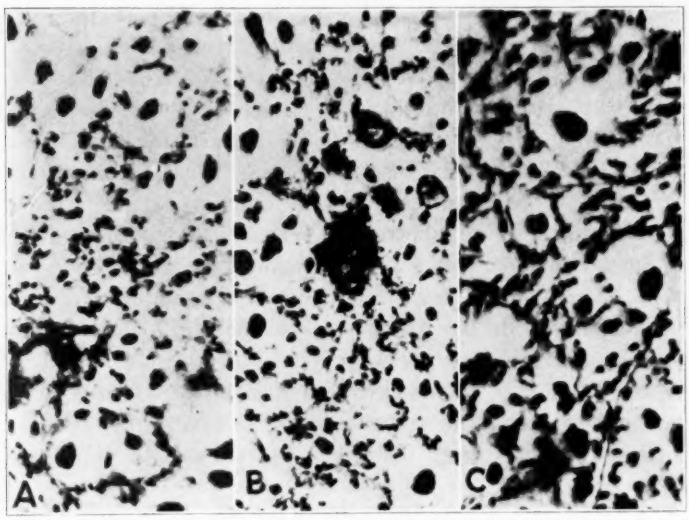
5. Levin, P. M.: The Exact Origin of the Corticospinal Tract in the Monkey, J. Comp. Neurol. **68**:411-422, 1938.

6. Ranson, S. W.: The Fasciculus Cerebrospinalis in the Albino Rat, Am. J. Anat. **14**:411-424, 1913.

7. McKibben, P. S., and Wheelis, D. R.: Experiments on the Motor Cortex of the Cat, J. Comp. Neurol. **56**:373-375, 1932.

8. Davenport, H. A.: Staining Paraffin Sections with Protargol: Experiments with Bodian's method; Use of *n*-Propyl and *n*-Butyl Alcohol in Hofker's Fixative, Stain Technol. **13**:147-160, 1938. Davenport, H. A.; McArthur, J., and Bruesch, S. R.: Staining Sections with Protargol: The Optimum p_H for Reduction; a Two-Hour Staining Method, ibid. **14**:21-26, 1939.

decided to try his method on the pyramidal tract. Suitable sections were made just rostral to the motor decussation in a series of 3 Negroes. Two were women, and 1 was a man; their ages averaged 24 years. In 2 of the 3 cases there were accidental injuries, and 1 patient succumbed quickly from an attack of pneumonia. We removed the brain stems within two hours post mortem. The area of each pyramidal tract was measured by means of an Edinger projection apparatus. Shrinkage was carefully determined for each specimen, so the values given for the areas are approximately normal. The stained axis-cylinders were studied as to size with an ocular micrometer. The diameter of obviously medullated fibers could be calculated by following the rule that the width of an axis-cylinder is equal to one-third the total diameter. For determining the number of fibers present in the tract a Whipple square was utilized. This square is subdivided into 196 small squares of equal size, and the average number of fibers per small square



Untouched photomicrographs of the pyramidal tract at a level just rostral to the motor decussation, showing the preponderance of small fibers and the similarity in appearance regardless of location. *A*, lateral; *B*, middle, and *C*, medial, area of the pyramidal tract. Magnification, × 900.

was determined. One eighth of the total fields in the brain of 1 woman and one sixteenth in the other 2 brains were counted, the fields being selected equal distances apart. By knowing the average number of fibers for each small square together with the entire area, the total number of fibers could be computed. All sections were examined and counted at a magnification of 1,125.

RESULTS AND COMMENT

All results and conclusions are based on a study of a pyramidal tract at a level just rostral to the motor decussation.

Reference to the accompanying figure will show that the predominant fiber of the human pyramidal tract is one of small caliber. The

large fibers, although they make a good appearance by their size, are not conspicuous numerically. We have calculated that only about 4 per cent of the fibers are more than 10 microns in diameter. By far the greater majority are between 1 and 5 microns, which agrees essentially with the findings of Häggqvist [3] in the monkey. Work in progress in this laboratory indicates that the characteristic fiber of the pyramidal tract of mammals is one of small dimensions. At least this has proved to be true in a series of 8 mammals studied to date. This suggests that for any given animal the pyramidal tract conducts slowly when it is considered as a whole.

The pyramidal tract on cross section presents the same picture, no matter what part is examined. In other words, the large fibers are not condensed in any one region of the pyramidal tract, but are scattered equally throughout. The same is true of the smaller fibers. It is taught that the fibers which are destined to go to the leg region

Statistical Data Showing the Numerical Values Obtained from a Silver Study of the Pyramidal Tract at a Level Just Rostral to the Motor Decussation

Specimen No.	Sex	Age, Yr.	Area of Pyramidal Tract, Sq. Mm.	Total No. of Pyramidal Tract Fibers	No. of Pyramidal Tract Fibers per Sq. Mm.
1	F	22	11.71	1,059,334	90,464
2	F	23	11.67	1,097,528	94,047
3	M	26	10.91	1,146,133	105,053
Average		24	11.43	1,100,998	96,521

are situated in the lateral portion of the tract and those which go to the arm and face regions in the medial part. If this is true, the fibers which go to the lower levels of the cord consist primarily of fibers of small diameter. Conversely, if the medial portion of the pyramidal tract possesses the fibers which go to the arm and facial regions, it contains proportionately as many large fibers as pass down to the lumbosacral segments of the cord.

The accompanying table shows the number of fibers which have been calculated to be present in the pyramidal tract of 3 human brains. The values obtained, over 1,000,000 for each brain, represents an increase of almost four times the previous count of Weil and Lassek.[2] This pronounced difference is believed to be due to a greater specificity of the new stain for the smaller fibers, and, second, to the fact that the fibers were counted at a higher level. One million fibers present in the human pyramidal tract does not seem an excessive number. A count of 1,200,000 myelinated fibers has been made in the optic nerve of man by Arey and Bickel,[9] and measurements which we have made

9. Arey, L. B., and Bickel, W. H.: The Number of Nerve Fibers in the Human Optic Nerve, Anat. Rec. (supp. 1) **61**:3, 1935.

of the optic nerve show that it has about the same area as has the pyramidal tract at a level just rostral to the decussation.

The counts obtained further augment the discrepancy between the fibers present and the number of Betz cells. As the situation now stands, there are approximately forty times as many fibers entering the spinal cord as there are Betz cells. The difference would be much greater if, in addition, the corticobulbar fibers were taken into account. One would not expect the Betz cells, which are the largest found in the cerebral cortex, to give origin to fibers of small caliber. As the fibers of small diameter are the predominant type in human pyramids, it is believed that by far the greater majority of pyramidal tract fibers must originate from cells of small size.

Experimental work, with the silver method and the numerical approach, is now in progress on a group of monkeys, in an attempt to localize the cells of origin of the pyramidal tract.

CONCLUSIONS

1. The predominant type of fiber in the human pyramidal tract is one of small caliber. Numerically, large fibers are scarce.

2. Neither small nor large fibers are aggregated in any one region of the pyramidal tract, but are equally dispersed throughout.

3. Slightly over 1,000,000 pyramidal tract fibers enter the spinal cord on one side.

4. It is believed that cells other than those of the Betz type give origin to a large percentage of pyramidal tract fibers and that these cells, wherever they may be located, are small.

5. The pyramidal tract, because of the preponderance of small fibers, should, on the whole, be a bundle which conducts slowly.

FOLLOW-UP STUDY OF FIVE HUNDRED PATIENTS WITH SCHIZOPHRENIA ADMITTED TO THE HOSPITAL FROM 1913 TO 1923

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There are a number of studies on the outcome of schizophrenia, but few in which there has been an opportunity to view the material over a long span of years. In view of the enthusiasm for insulin and metrazol therapy, it would seem of advantage to have statistics on the outcome of schizophrenia in patients not treated by these methods. Late in 1936 a project was instituted at the Henry Phipps Psychatric Clinic for a study of the status of former patients.[1] The plan calls for a review of the 8,300 patients admitted to the clinic during its existence, with particular reference to scrutiny of the case material and study of the long term outcome. After preliminary organization of the material, contact with the patients was begun in 1937, twenty-four years after the first patient was admitted. During the two years that this project has been under way, repeated efforts to secure information in the early cases has brought the interval to nearly twenty-six years after the admissions of 1913. Since a good history of some of these early patients was obtained previously, we have for some of them a comprehensive record of nearly fifty years.

As a sample of the large project, this paper deals with a selected group of 500 patients exhibiting a typical picture of parergasic disorder (literally, twist behavior with fundamental or fancy-born incongruities more or less foreign to average mature waking life, commonly known by the less inclusively descriptive term of schizophrenia, or dementia praecox). This group is made up of the patients admitted between May 1913, when the clinic first accepted patients, and May 1923. We have excluded from the group all cases in which the diagnosis of parergasia was unclear, cases in which the condition was diagnosed in the older terminology as "allied to dementia praecox," all cases in which subsequent follow-up information showed the original diagnosis to be uncertain or mistaken and all cases in which the history was inadequate or unsatisfactory, owing to a brief stay, language difficulty or other reasons.

1. This study was made possible by the help of the John and Mary R. Markle Foundation.

The present status of the patients has not always been easy to obtain. Accurate descriptions are often difficult to secure from the history as reported by the families. The misleading factor in the study lies in the fact that the most definite findings are adverse because the best available records are those obtained on permanently hospitalized patients. In the cases in which there have been remissions or recoveries descriptions frequently fail to do justice to the patients who were paroled perhaps for as long as two years before final discharge. When the patient's progress has been unfavorable families are sometimes reluctant to give adequate information. Some patients have requested that they be not written to or reminded of their former illness.

Nonetheless, we believe that we have had gratifying results in the responses to our inquiries. Of the 500 cases selected for the study, we have been unable to get adequate facts in only 44. These cases have been used only for correlation of data covering the period previous

TABLE 1.—*Results of Follow-Up Investigation of Patients Admitted from May 1913 to May 1923*

	Males	Percentage	Females	Percentage	All Patients	Percentage
Followed to date	96	19.2	126	25.2	222	44.4
Followed until not traceable	61	12.2	73	14.6	134	26.8
Followed until death	47	9.4	53	10.6	100	20
Followed until not traceable (less than 1 year*)	20	4.0	24	4.8	44	8.8
	224	44.8	276	65.2		

* Data not considered sufficient for analysis of follow-up information.

to discharge from the clinic. Concerning 456 patients we have some statement of the course of the disease, ranging from one to twenty-six years after hospitalization. Table 1 shows the results of attempts to secure follow-up information.

MATERIAL

There is no restriction on admission to this clinic except for the voluntary choice of admission and ability to accommodate the patient. Patients who prove disturbed beyond the possibility of the equipment to protect adequately and those who show obvious signs of chronicity are later discharged to more suitable hospitals, to give room for pateints more likely to be benefited by the intensely personal type of therapy which the clinic has to offer. Some patients are admitted because of their interest for research, because they present unusually challenging therapeutic possibilities or because they can be used in teaching. The material in our case histories, on the whole, bids fair to offer a complete range of the parergasic disorder, the outcome varying between the extremes of recovery at the best previous level and hospitalization at an almost vegetative existence.

The larger project embarked on aims to do more than present merely the post-hospital course of the condition. Part of the project includes also an abstract of the total record of each case with a statement of the genetic-dynamic factors, heredity, constitution and personality, family setting, life adjustment to events,

somatic disorders as part of the illness and presence or absence of obvious precipitating events, the preoccupations of the patient, the length of stay in the hospital and the subsequent course. In every case abstract there is little or no use of adjectives or merely interpretative descriptive terms. Statements of fact illustrative of the picture or verbatim reports of typical content are used instead. A brief statement may therefore be employed at this point to describe the various factors within the person and within the illness which have been singled out in every case selected for this study. Since these facts have been incorporated in the work sheets prepared for the present study, they are enumerated in table 2.

This material has been compiled from the entire series of 500 cases. It will be evident from table 2 that in the individual case the picture is highly personal and that the factors operating are varied and multifarious. In 11.8 per cent of cases flurries of disturbances were clearly present before the onset of the actual psychosis. These flurries were transient, with usually not more than temporary interruption of occupation or obvious reduction of efficiency. They occurred without consistent habitual change of personality and appeared under situations of undue difficulty, such as pregnancy, menstrual instability and religious experiences, and were expressed as brooding, insomnia, temporary agitation over disappointment in love and ideas of being talked about or discriminated against.

TABLE 2.—*Incidence of Positive Dynamic Factors (500 Cases)*

	Males	Percentage	Females	Percentage	Both Sexes	Percentage
Flurries before onset	23	4.6	36	7.2	59	11.8
Personality change before onset	46	9.2	31	6.2	77	15.4
Personality difficulty	139	27.8	140	28.0	279	55.8
Family difficulty	76	15.2	132	26.4	208	41.6
Somatic difficulty	43	8.6	68	13.6	111	22.2
Precipitating events	152	30.4	212	42.4	364	72.8

Fifteen per cent of the patients showed clear personality change before the onset of the psychosis. The onset of the parergasia was placed at the time when it became noticeable to the patient or to persons in his environment that he was in marked psychobiologic distress. The onset may be preceded by a more vague condition, such as noticeable apathy, puzzling, explosive irritability, unrest, fears, poor concentration, seclusiveness, minor oddity in behavior, more or less vague dissatisfaction with environment or excessive drinking. During this period the patient is able to be productive. The actual onset occurs when he is unable to continue his former level of productivity and abruptly terminates it, showing signs of delusions or hallucinations.

We have been struck by the occurrence in 55.8 per cent of our cases of personality difficulties, by which we mean constellations of difficulties present from earliest life, such as stammering, tics, temper tantrums, enuresis, easy fainting or vomiting, or stubborn, shy, seclusive dependent or self-conscious makeup, developing with a sense of inferiority, excessive jealousy, antagonism, daydreaming or ambitions beyond reasonable capacity, often with worries over masturbation, homosexual tendencies, sexual perversions, difficulty in adaptation to group or occupation or other signs of conspicuously inadequate adjustment to the environment.

Family difficulties were prominent (in 41.6 per cent) and were considered to be present when parents were obviously immoral or criminal, were separated or dead, had conflicting religions, or were rigid, quarrelsome, dominating, alcoholic or brutal in behavior. Other family difficulties frequently noted included a sense

of shame or burden because of poverty, a sense of being unduly favored or discriminated against, with mental or severe personality difficulty within the family.

Somatic difficulties preceding the onset of the illness were present in about one fifth (22.2 per cent) of our cases.

Precipitating events were extremely common (in 72.8 per cent) and were concerned predominantly with sex and love, masturbation, homosexual manifestations, illicit sex relations, disturbing sex experiences and impotence. Disappointment in love; actual difficulties within marriage, such as infidelity, indifference, discord, disillusionment and pregnancy; reaction to puberty, and general social and occupational environment all acted as immediate precipitating events.

METHOD

The method of follow-up study employed was to trace the patient's present status by the use of a letter of inquiry to the patient, relatives or family physician;

TABLE 3.—*Sources of Follow-Up Information*

	No. of Patients
Hospital report only	165
Letter only	88
Hospital report and letter	48
Social service visits only	60
Hospital report and social service visits	40
Staff doctor's interview only	4
Staff doctor's interview, hospital report and letter	5
Staff doctor's hospital report and social service visits	2
Staff doctor's interview and letter	15
Staff doctor's interview and social service visits	12
Staff doctor's interview and hospital report	13
Letter and social service visits	3
Social service visits, letter and hospital report	1
	456
Totals: Hospital reports	272
Letters	157
Social service visits	118
Staff doctor's interviews	51

a personal interview by a staff member, or an interview with the patient or family by a social worker employed for this project. A number of patients were followed by all three methods. For the 456 patients chosen, therefore, the follow-up information was considered adequate for this study, only persons being excluded for whom partial or inadequate facts were obtained. In table 3 the sources of follow-up information are indicated.

DESCRIPTION OF TERMS USED IN CLASSIFICATION OF RESULTS

Evaluation of the status of the patient at any given time and the rendering of it in a word or phrase are difficult. Much depends on the environment in which the patient is found. It would be a simple matter to say that he is hospitalized or not hospitalized, but, aside from the practice of protracted parole, one finds many parergasic persons doing intricate and unsupervised work within a hospital, entertaining the while some bizarre delusions which would soon make life on the outside extremely uncomfortable. Some patients kept at state hospitals have become free from symptoms and might succeed productively on the outside if the home environment were more favorable. On the other hand, there are

patients at home who are able to do nothing at all, but are protected by the family from any demands on them. A psychotic woman keeping house or a man returned to the family farm may be in a more unproductive and disturbed condition than some patients retained in hospital who are described as making a "good hospital adjustment." Families sometimes report as completely recovered patients who are still having evident difficulties. Then there is the extreme of the few patients who earn an adequate living, although they may continue to be hallucinated. A few patients have adjusted in an environment in which the social group accepts "spells" and various occult manifestations as within the realm of normal possibility. If the economic times are good enough to provide frequent changes of job, a patient may support himself indefinitely without too florid delusions or psychotic crises. Patients may have remissions and relapses who during intervals carry on intricate work. In order to do justice to the wide range of functioning outside a hospital, we have selected the following terms as the minimum of descriptive words necessary to describe the status of these patients. We have used the term "productive" rather than "work." We consider productive not only the worker as an earner but the woman who is able to manage her home and maintain her share of social life or a student able to carry on his education.

Recovery to the Previous Level (R P L).—Our best adjusted patients are described as "recovered to the previous level." For some of these patients the previous level was never an enviable adjustment to life. However, this term is used to describe their best previous level, and some have assured us that they were better than ever before in their lives.

Recovery at a Reduced Level (R R L).—This term indicates that the person is free from symptoms and is productive, but in an environment less taxing and at work that is less intricate or responsible than before.

Productive with Symptoms (P S).—Some patients, productive with symptoms, sustain themselves, at least temporarily, in spite of a surprising number of hallucinations and suspicions, which as a rule eventually fade out or become florid.

Partially Productive with Relapses (P P R).—Productive patients with relapses keep out of hospitals, but have flurries or episodes which temporarily incapacitate them.

Productive Family Invalid (P F I).—Such a patient is in a highly protected environment, is without unpredictable flare-ups and is able to do odd jobs on good days, or he may be able to travel extensively with his family.

Family Invalid (F I).—The patient is frequently of the vegetative, harmless type, without dangerous impulses, but is too disorganized to fix his attention on simple tasks. The patient may, on the other hand, be hospital material in a home able to support adequate nursing and other attention.

Productive Hospital Invalid (P H I).—More productive, but probably more unpredictable, is the productive hospital invalid. The term "productivity" in case of this patient is widely inclusive. It may involve consistent, unsupervised work of a high grade, in the case of a delusional or hallucinated patient. It may mean the more or less dependable help in the linen room or field gang. This patient is usually described as making a "good hospital adjustment."

Hospital Invalid (H I).— The term "hospital invalid" is used in some cases in which there is no indication that the patient is able to do more than push a floor polisher or engage in other almost automatic activity. He may show no deterioration, but refuse to participate in activity.

Deteriorated Hospital Invalid (D H I)—These persons are the most disturbed or most helpless of all patients. The term is obvious.

RESULTS

In discussing the results of this investigation we shall start with a statement concerning these patients at the time of their entry to and discharge from the Phipps Clinic.

It will be seen from table 4 that at the time of discharge from the clinic 42.7 per cent of our patients were well or improved. Slightly more than half the total number (57.34 per cent) left the hospital unimproved. Many of these patients were transferred to other hospitals, and their subsequent course will be shown later.

TABLE 4.—*Condition on Discharge from the Henry Phipps Psychiatric Clinic (500 Patients)*

	Males	Females	Both Sexes	Percentage of Males	Percentage of Females	Percentage of Both Sexes
Well	22	40	62	4.25	7.72	11.97
Improved	66	90	156	12.74	17.37	30.11
Unimproved	140	157	297	27.03	30.31	57.34
Dead	2	1	3	0.39	0.19	0.58

TABLE 5.—*Age at Onset of Illness (500 Cases)*

Age	Males	Percentage	Females	Percentage	Both Sexes	Percentage
11-20	48	10.53	48	10.53	96	21.05
21-30	103	22.59	130	28.51	233	51.1
31-40	33	7.24	58	12.72	91	19.96
41-50	13	2.85	18	3.95	31	6.8
51-60	1	0.22	4	0.88	5	1.1

The findings recorded in table 4 actually give no intimation of the full course of the disorder. The subsequent progress of the condition will be seen to be so variable that any statistics compiled on the condition at discharge from a hospital are likely to be grossly misleading.

Patients included in this study were under treatment at the clinic for varying lengths of time, the average period being as follows:

Males ..... 3¾ mo.
Females ..... 2½ mo.

Since almost half of the patients under treatment responded with improvement, the shorter length of stay in a hospital for the female patients may indicate a more favorable course for women than for men.

The age at onset of the illness, expressed in decades, is summarized in table 5, from which it will be seen that by far the largest number of patients (51.1 per cent) showed the onset of the illness between the ages of 21 and 30.

The age at the first hospitalization, expressed in decades, is summarized in table 6, from which it will be seen that the largest incidence of hospitalization was preponderately in the decade from 21 to 30 and the next largest in the decade from 31 to 40.

We were interested in the length of time taken for development of the acute psychosis, and in table 7 the durations of the periods of onset for the various age groups are averaged. It will be seen from this table that the average period of onset for the entire group was thirteen and a half months. The longest average span of development was in the age group in which the first hospitalization occurred between the ages of 41 and 50, in which it is seen that the illness took slightly less than two years for its development. There were, of course, marked

TABLE 6.—*Age at First Hospitalization (500 Cases)*

Age	Males	Percentage	Females	Percentage	Both Sexes	Percentage
11-20	32	6.40	47	9.40	79	15.80
21-30	125	25.00	123	24.60	248	49.60
31-40	46	9.20	70	14.00	116	25.20
41-50	16	3.20	30	6.00	46	9.20
51-60	5	1.00	6	1.20	11	2.20

TABLE 7.—*Span of Onset at Time of First Hospitalization*

Decade of Life	Period of Onset		Average Period of Onset (Mo.)
	Males (Mo.)	Females (Mo.)	
11-20	7¼	6¾	7
21-30	12½	10¼	11+
31-40	15¼	15¾	15½
41-50	22¼	21¾	22
51-60	10	15¼	12+

Average period for whole group, 13½ months

individual variations within these groups, ranging from an acute developmental period of a few days to a period of progressive change of twelve years, in the case of 1 patient, before precipitation of the acute psychosis.

We were interested in knowing whether the age at which the disorder first makes its onset has any relation to the ultimate outcome of the disease. In table 8 the outcome is studied in relation to the age at the first onset of the disorder.

If in table 8 one compares the number of patients in hospitals with the number out of hospitals, it will be seen that in the group in which the onset of illness occurred between the ages of 11 and 20 almost twice as many patients remained hospitalized as were discharged (13.38: 7.68 per cent). In the age group of from 21 to 30 the preponderance of patients remaining in hospitals (28.7: 22.3 per cent) was

smaller. In the age group of from 31 to 40 there was a slight preponderance in the number of patients who remained out of hospital (10.3: 9.65 per cent). Thus, it seems that the best chance of remaining out of hospital is for persons in whom the onset is in the decade from 31 to 40 years of age.

On the basis of the status of these patients many years after their first hospitalization, a classification into three groups is shown in table 9.

TABLE 8.—*Age at First Onset in Relation to Ultimate Outcome (456 Cases)*

11-20 Yr.		21-30 Yr.		31-40 Yr.		41-50 Yr.		51-60 Yr.	
Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
Outcome: Patients Out of Hospitals									
14	21	34	68	17	30	8	6	1	2
3.07%	4.61%	7.46%	14.91%	3.73%	6.58%	1.75%	1.32%	0.22%	0.44%
Both Sexes		Both Sexes		Both Sexes		Both Sexes		Both Sexes	
35 (7.68%)		102 (22.37%)		47 (10.31%)		14 (3.07%)		3 (0.66%)	
Outcome: Patients in Hospitals									
34	27	69	62	16	28	5	12	..	2
7.46%	5.92%	15.13%	13.6%	3.51%	6.14%	1.10%	2.63%	.....	0.44%
Both Sexes		Both Sexes		Both Sexes		Both Sexes		Both Sexes	
61 (13.38%)		131 (28.73%)		44 (9.65%)		17 (3.73%)		2 (0.44%)	

Outcome: Relation to Age of Onset

	11-20 Yr.			21-30 Yr.			31-40 Yr.			41-50 Yr.			51-60 Yr.		
	Males	Females	Both Sexes	Males	Females	Both Sexes	Males	Females	Both Sexes	Males	Females	Both Sexes	Males	Females	Both Sexes
RPL	4	13	17	18	39	57	8	22	30	5	2	7	1	1	2
%	0.88	2.85	3.73	3.95	8.55	12.50	1.75	4.82	6.58	1.10	0.44	1.54	0.22	0.22	0.44
RRL	3	4	7	2	6	8	1	0	1	..	..	0	..	..	..
%	0.66	0.88	1.54	0.44	1.32	1.75	0.22	....	0.22	....	....	....	....	....	....
PS	3	1	4	3	6	9	2	5	7	2	2	4	..	1	..
%	0.66	0.22	0.88	0.66	1.32	1.98	0.44	1.10	1.54	0.44	0.44	0.88	....	0.22	....
PPR	2	..	2	2	7	9	..	..	..	..	1	1	..	..	..
%	0.44	....	0.44	0.44	1.54	1.98	....	....	....	....	....	....	....	....	....
PFI	1	..	1	2	2	4	..	..	..	..	0	0	..	..	..
FI	1	3	4	7	8	15	6	3	9	1	1	2	..	..	..
%	0.44	0.66	0.88	1.54	1.75	3.29	1.32	0.66	1.98	0.22	0.22	0.44	....	....	....
PHI	11	2	13	10	7	17	5	1	6	..	2	2	..	..	..
%	2.41	0.44	2.85	2.19	1.54	3.73	1.10	0.22	1.32	....	....	0.44	....	....	....
HI	10	12	22	44	35	79	11	20	31	5	7	12	..	2	2
%	2.19	2.63	4.82	9.65	7.68	17.32	2.41	4.38	6.80	1.10	1.54	2.63	....	0.44	0.44
DHI	13	13	26	15	20	35	0	7	7	..	3	3	..	..	..
%	2.85	2.85	5.70	3.29	4.39	7.68	....	1.54	1.54	....	0.66	0.66	....	....	....

The first group is a series of 222 cases in which the patients were followed for an average of twenty years. The second group consists of 134 cases in which the span of follow-up study was not as long; it averaged nine years. The third group consists of 100 cases in which the patients were found to have died during the interval, which ranged from nine to twenty years.

Scrutiny of table 9 reveals some interesting facts. The first striking observation is that patients observed for the twenty year period showed a distinctly less favorable outcome both as to number of recov-

eries and as to the total time of hospitalization than patients followed only for the nine year period. After twenty years 27.03 per cent of the patients show recovery to their previous level; 57.6 per cent are hospitalized. When, however, one examines the group who are on the average nine years removed from their first hospitalization, one finds that 35 per cent have recovered to their previous level and only 35 per cent are still in hospital. The difference lies essentially in the fact that a considerable number of patients who were partially recovered and were able to be kept at home have had, during the latter part of the twenty year span, to be returned to a hospital. These

TABLE 9.—*Status of Outcome at Nine Levels of Adjustment*

	Average Follow-Up Period of 20 Years 222 Patients			Average Follow-Up Period of 9 Years 134 Patients			Patients Followed Until Death 100 Patients			
Level	Male	Female	Both Sexes	Male	Female	Both Sexes	Male	Female	Both Sexes	Total
RPL	16	44	60	24	23	47	2	3	5	112
Percentage	7.21	19.80	27.03	17.91	17.16	35.07	2	3	5	24.56
RRL	4	5	9	1	6	7	1	0	1	17
Percentage	1.80	2.25	4.05	0.75	4.48	5.22	1	..	1	3.74
PS	4	6	10	6	5	11	0	4	4	25
Percentage	1.80	2.70	4.50	4.48	3.73	8.21	..	4	4	5.48
PPR	3	3	6	1	4	5	0	1	1	12
Percentage	1.35	1.35	2.70	0.75	2.99	3.73	..	1	1	2.64
PFI	2	2	4	1	0	1	0	0	0	5
Percentage	0.90	0.90	1.80	0.75	....	0.75	..	..	..	1.10
FI	3	2	5	8	8	16	5	5	10	31
Percentage	1.35	0.90	2.25	5.97	5.97	11.94	5	5	10	6.80
PHI	26	10	36	1	0	1	0	1	1	38
Percentage	11.71	4.50	16.22	0.75	....	0.75	..	1	1	8.34
HI	17	21	38	15	21	36	36	35	71	145
Percentage	7.66	9.46	17.12	11.19	15.67	26.87	36	35	71	31.80
DHI	21	33	54	4	6	10	3	4	7	71
Percentage	9.46	14.86	24.32	2.99	4.48	7.46	3	4	7	15.58
									Total	456

facts are more clearly brought out if one groups the outcome under four categories, as in table 10. There it will be seen that, in addition to the recovered patients, a second group who are partially productive but not entirely well contains a considerable number of patients (17.16 per cent). Another group (12.6 per cent) consists of patients who after nine years are being taken care of at home, but who are essentially nonproductive.

When the entire group of 456 patients is considered, the most immediate fact is that 44.3 per cent are out of hospital at present; 55.7 per cent are in a hospital. Thus, it will be seen that, in addition to 24.56 per cent of the patients who are recovered, 11.8 per cent are at a productive level, although it can hardly be claimed that they are entirely well. Eight per cent of the patients are being managed at home, but of these only a few (3.7 per cent of the total) are productive.

Thus far in the study, we have shown what happens to these patients at the time of their discharge from the hospital and at varying periods thereafter. This fails to do justice to their progress and course

TABLE 10.—*Status of Outcome in 456 Patients*

Level		Average Follow-Up Period of 20 Years (222 Patients)			Average Follow-Up Period of 9 Years (134 Patients)			Patients Followed Until Death (100 Patients)			Grand Total
		Male	Female	Both Sexes	Male	Female	Both Sexes	Male	Female	Sexes	
Four Levels of Adjustment											
Recovered	RPL	16 7.21%	44 19.80%	60 27.03%	24 17.91%	23 17.16%	47 35.07%	2 2%	3 3%	5 5%	112 24.56%
Partially productive	RRL PS PPR	11 4.95%	14 6.31%	25 11.26%	8 5.97%	15 11.19%	23 17.16%	1 1%	5 5%	6 6%	54 11.8%
Nonproductive	PFI FI	5 2.25%	4 1.80%	9 4.05%	9 6.72%	8 5.97%	17 12.69%	5 5%	5 5%	10 10%	36 8%
Hospitalized	PHI HI DHI	64 28.83%	64 28.83%	128 57.66%	20 14.93%	27 20.15%	47 35.07%	39 39%	40 40%	79 79%	254 55.7%
In or Out of Hospital											
		Male	Female	Total	Male	Female	Total	Male	Female	Total	Grand Total
Out of hospital		32 7.02%	62 13.30%	94 20.61%	33 7.24%	56 12.28%	87 19.08%	8 1.75%	13 2.85%	21 4.61%	202 44.30%
In hospital.....		74 16.23%	64 14.04%	128 28.07%	20 4.38%	27 5.92%	47 10.31%	39 8.55%	40 8.77%	79 17.32%	254 55.70%

TABLE 11.—*Status of 456 Patients with Regard to Course of Hospitalization*

	Twenty Year Period of Observation			Nine Year Period of Observation			Observation Until Death			Total No. of Patients		
	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total
Never readmitted to hospital.....	20	40	60	35	36	71	6	12	18	61	88	149
Percentage.....	4.38	8.78	13.16	7.68	7.90	15.58	1.32	2.63	3.95	13.38	19.30	32.68
Later readmitted but finally out of hospital.....	12	22	34	6	10	16	2	1	3	20	33	53
Percentage.....	2.64	4.84	7.48	1.32	2.20	3.52	0.44	0.22	0.66	4.40	7.24	11.64
Later readmitted and finally in hospital....	28	23	51	11	12	23	15	12	27	54	47	101
Percentage.....	6.15	5.04	11.19	2.41	2.63	5.04	3.28	3.63	6.91	11.85	10.31	22.16
Never out of hospital	36	41	77	9	15	24	24	28	52	69	84	153
Percentage.....	7.90	8.99	16.89	1.98	3.28	5.26	5.26	6.15	11.41	15.13	18.42	33.55

throughout the years, and on examination of these data one finds great variability in the course of the disorder as regards rehospitalization. We have summarized the actual facts concerning readmission in table 11, in which it will be seen that 32.6 per cent of all patients were not readmitted to any hospital after discharge from this clinic; 33.5 per cent of the patients were never able to leave a hospital.

It will be seen that a considerable number of patients were later readmitted to hospitals, some to be finally discharged and some for permanent hospitalization. These facts, in the 456 cases, are perhaps better expressed as follows:

Males:	Percentage
Of 204 admitted, 135 were discharged	66.17
Of 135 discharged, 74 were readmitted	54.86
Of 74 readmitted, 20 were finally out of hospital	27.02
Females:	
Of 252 admitted, 168 were discharged	66.66
Of 168 discharged, 80 were readmitted	47.61
Of 80 readmitted, 33 were finally out of hospital	40.12

Table 11 shows clearly that the course of the illness for all but a third of our patients (32.68 per cent) has meant readmission to a hospital at a subsequent date. An additional 11.6 per cent had to be readmitted to a hospital, but were finally discharged and have been able to stay out of a hospital for the duration of this survey. At the time of this survey, therefore, more than half the series of patients (55.7 per cent) have remained in or have been readmitted to a hospital. It seems necessary therefore to reassert the striking fact of this survey: that a long term view of this disorder shows frequent, repeated or permanent hospitalization for over half the group. A long term view of parergasia is obligatory in the evaluation of any therapeutic procedure with respect to the outcome of the disease. In the enthusiasm for the new methods of treatment with insulin shock and metrazol convulsion it will be necessary to delay evaluation until a sufficient length of time, not measured in one or two years, has elapsed. This seems to be the most striking fact elicited by this study. If, now, one turns to the graphic representation of the course of hospitalization for the 222 patients whom we have been able to follow for an average period of twenty years, certain striking facts will be seen to emerge (charts 1 and 2).

For the majority of the patients who have recovered to their previous level, a single brief period of hospitalization is the rule. There are exceptions to this statement in that one fourth of the total number had a period of readmission to a hospital. One patient, after ten years of psychotic behavior in a hospital, appears to have been completely recovered for eight years. Another patient, after eight years of hospitalization, appears to have been completely recovered for fourteen years. In a few other cases there have been as many as five hospitalizations before recovery was effected. Thus, a second or even a third or fourth hospitalization does not necessarily spell poor prognosis. Nonetheless, it is striking that the period of hospitalization for the recovered group is for the most part less than a year. Even in this

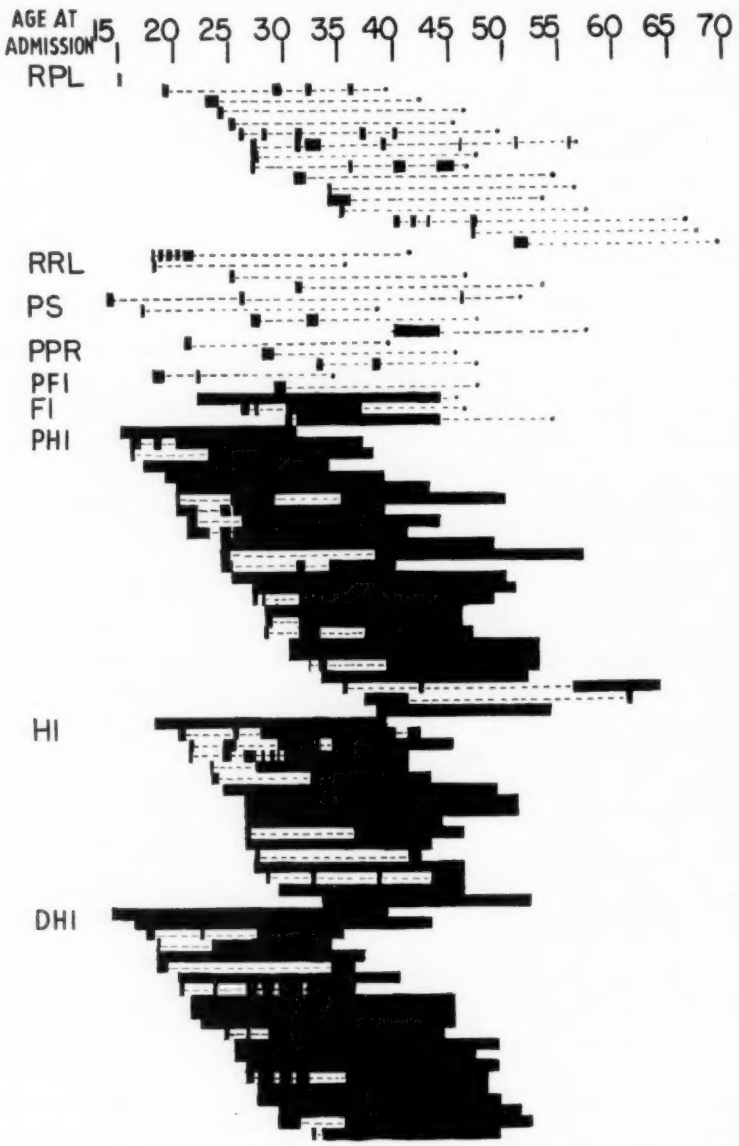

Chart 1.—Course of hospitalization charted according to outcome of the disease in a group of 96 male patients observed for a period of twenty years.

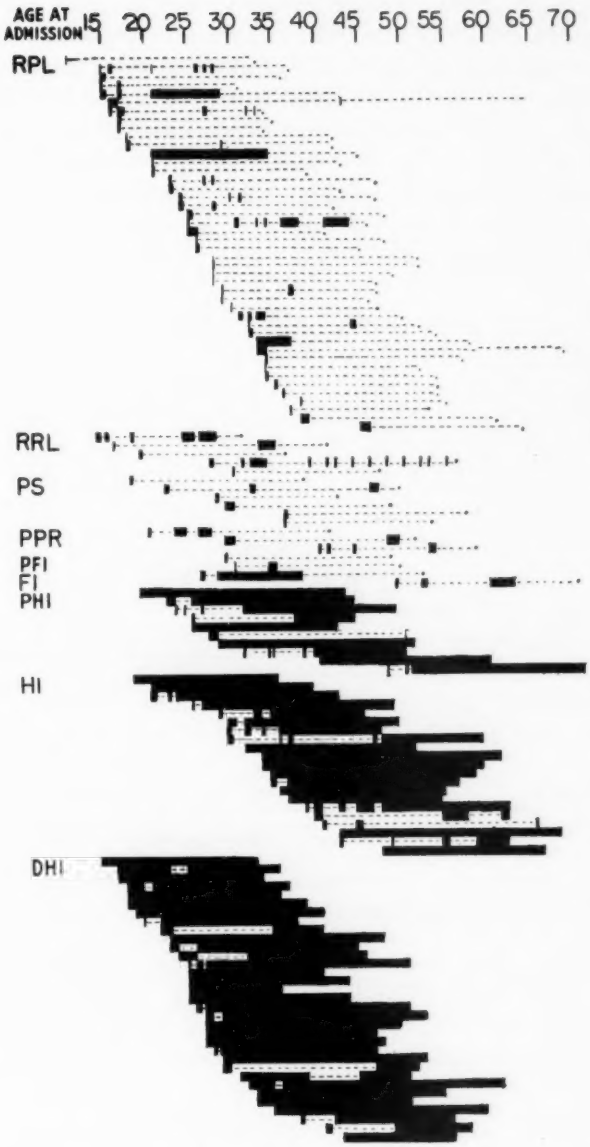

Chart 2.—Course of hospitalization charted according to outcome of the disease in a group of 126 female patients observed for a period of twenty years.

group, however, intervals of well-being of as long as ten years may occur between hospitalizations. Repeatedly, one sees long intervals of from three to ten years before a second hospitalization is necessary.

In marked contrast to the relatively brief period of hospitalization and to the single admission of the majority of the recovered patients are the findings for the group of permanently hospitalized patients. For the most part these persons show a protracted and uninterrupted period of hospitalization from the time of first admission. However, gaps of time between the first and the permanent hospitalization occur in 35

TABLE 12.—*Cause of Death in 100 Cases of Schizophrenia*

Cause of Death	Males	Females	Both Sexes
Tuberculosis	11	16	27
Respiratory disease	5	8	13
Suicide	7	4	11
Cardiac disease	3	4	7
Gastrointestinal disease	1	5	6
Carcinoma	1	5	6
Exhaustion (excitatory or catatonic)	4	0	4
Genitourinary disease	2	2	4
Peritonitis	2	0	2
Apoplexy	1	1	2
Operations	1	0	1
Unknown cause	10	7	17
	48	52	100

TABLE 13.—*Age at Death, Expressed in Decades, in 100 Cases of Schizophrenia* *

Age	Males	Females	Both Sexes
11 to 20	1	1	2
21 to 30	18	13	31
31 to 40	15	12	27
41 to 50	9	16	25
51 to 60	3	7	10
61 to 70	1	4	5
	47	53	100

* The youngest patient was 17; the oldest, 69.

per cent of the group, and may range from a few months to extremes, in 3 cases, of ten, fourteen and seventeen years. In the cases in which the patients do not recover a long period of initial hospitalization is the rule, although long periods out of hospital may occur before there are ultimate hospitalization and deterioration. Permanent recovery, therefore, is difficult to predict, even after long years of apparent well-being. These findings tend to reemphasize the fact that extreme caution must be exercised in offering prognosis in cases of schizophrenia.

We plan an extensive later study of these two large groups in the hope of analyzing the factors that make for or oppose recovery.

We have previously stated that in 100 of our 500 cases the course ended in death. The cause of death and the decade in which death occurred are given in tables 12 and 13, respectively.

It will be seen from tables 12 and 13 that the largest number of deaths occurred in the age decade from 21 to 30 and that the chief cause of death was tuberculosis.

SUMMARY

A survey of 500 schizophrenic patients has been made, 222 of whom have been followed for an average of twenty years.

In all but 44 of the patients, the survey has obtained facts concerning the progress of the patient.

The case material is extremely variable and is analyzed for the outstanding factors within the patient and within the environment.

At the time of discharge from the Phipps Clinic, 42.7 per cent of the patients were well or improved; slightly more than half (57.34 per cent) left the hospital unimproved.

The course of the illness seems more favorable for women than for men.

At the end of twenty years the picture is less favorable than at the end of nine years or at the time of discharge. After twenty years, 27 per cent of patients show recovery; an additional 13 per cent give evidence of some productivity.

There is great variability in the course of the disorder as regards rehospitalization; 33.5 per cent of the total series of patients were never able to leave a hospital; 32.6 per cent were never readmitted to any hospital.

While rehospitalization is frequent, this does not necessarily affect the final outcome.

A relatively brief period of hospitalization is the rule for patients who recover.

Evaluation of any therapeutic method obligatorily waits on long term observation.

The largest number of deaths occurs in the age decade of 21 to 30. The chief cause of death is tuberculosis.

Case Reports

PINEALOMA OF DIFFUSE EPENDYMAL ORIGIN

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The pineal body makes its first appearance in man at about the second fetal month as a cellular mass and an evagination in the roof of the diencephalon. The two structures fuse, and the cavity of the united mass deepens to form the pineal recess. The cells lining the recess develop cilia and come to resemble the ependyma closely. The histogenesis of the pineal body itself is complicated, but the parenchymal cells seem to develop from ependymal anlages. Several facts support this opinion, in particular the occurrence of tubules in the fetal pineal body and the possession of blepharoplasts and processes by pineal cells. At about the sixth fetal month, masses of small, darkly staining cells, thought by Globus and Silbert,[1] Bailey [2] and others to be mesenchymal in origin, appear in the pineal body in conjunction with connective tissue and blood vessels. These smaller cells form a mosaic pattern, in the interstices of which the larger parenchymal cells are congregated. According to Globus and Silbert, this mosaic pattern is a characteristic of fetal stages of development, but it is often not easily seen in the adult organ.

The larger parenchymal cells have unique morphologic features which render them recognizable wherever found. They have been described by del Rio-Hortega [3] as having scanty or abundant cytoplasm and round or oval, vesicular nuclei, which are often deformed by wrinkles. Larger cells may contain double nuclei, and occasional monster cells may be seen in which the multiple nuclei tend to lie in the periphery of the cytoplasm. Chromatin is present as fine granules; the nucleolus is large and prominent. Blepharoplasts are frequent. Many nuclei contain characteristic large globules, which stain heavily with silver or hematoxylin, as first described by Dimitrova.[4] The parenchymal cells have processes which terminate in free endings or in bulbs lying on blood vessels or connective tissue septums. Del Rio-Hortega said that these cells may be grouped in perivascular rosette or palisade formations.

Read at a meeting of the Chicago Neurological Society, Feb. 16, 1939.

From the Laboratory of Neurohistology of the Illinois State Department of Public Welfare.

1. Globus, J. H., and Silbert, S.: Pinealomas, Arch. Neurol. & Psychiat. **25**:937 (May) 1931.

2. Bailey, P., in discussion on Globus and Silbert.[1]

3. del Rio-Hortega, P.: Pineal Gland, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 2, p. 637.

4. Dimitrova, Z.: Recherches sur la structure de la glande pinéal chez quelques mammifères, Névraxe **2**:259, 1901.

Tumors arising from the pineal body have been described since 1800.[5] They occur in lower animals as well as in man, as demonstrated by Schlotthauer and Kernohan,[6] who found a pinealoma in a silver fox. The association of the larger parenchymatous with the smaller, dark-staining cells constitutes a characteristic feature of these tumors. The smaller cells form a mosaic in some tumors; in others they are more diffusely distributed. They usually tend to collect around blood vessels, lying in a network of reticulin fibers. The larger, parenchymatous cells exhibit in these tumors some or all of their unique morphologic characteristics, including blepharoplasts, blunt processes with end bulbs, large nuclei with prominent nucleoli and particularly the spherular intranuclear masses, which are usually more common in tumors than in the normal pineal body. Multinucleated giant cells are often present, and in rapidly growing tumors both mitotic and amitotic cell division is frequent. Pinealomas have been described which contained nerve cells,[7] spongioblasts [2] and perivascular palisades similar to those seen in the ependymomas.[8]

The pinealomas are usually cellular and fragile tumors which invade and destroy adjacent structures and penetrate the ventricles.[9] Occasionally they may spread to the ependyma or subarachnoid space by implantations through the cerebrospinal fluid, as reported by several authors.[10] Thus, the cranial and spinal nerves may become infiltrated by the tumor cells.[11] Groff recorded a remarkable case in which a

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6. Schlotthauer, C. F., and Kernohan, J. W.: A Glioma in a Dog and Pinealoma in a Silver Fox, Am. J. Cancer **24**:350 (June) 1935.

7. Horrax, G., and Bailey, P.: Pineal Pathology: Further Studies, Arch. Neurol. & Psychiat. **19**:394 (March) 1928.

8. (*a*) Glaser, M. A.: Tumors of the Pineal, Corpora Quadrigemina and Third Ventricle: Inter-Relationship of Their Syndromes and Their Surgical Treatment, Brain **52**:226 (July) 1929. (*b*) de Busscher, J.: Tumeur épiphysaire; envahissement des ventricules cérébraux, J. belge de neurol. et de psychiat. **36**:375 (June) 1936.

9. Horrax, G., and Bailey, P.: Tumors of the Pineal Body, Arch. Neurol. & Psychiat. **13**:423 (April) 1925. Glaser.[8a] Globus, J. H.: Pinealoma with Supratentorial Extension and Manifestations of Disrupted Temperature Regulation, in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues, New York, International Press, 1932, vol. 2, p. 491. de Busscher.[8b]

10. Berblinger, W.: Zur Kenntnis der Zirbelgechwülste, Ztschr. f. d. ges. Neurol. u. Psychiat. **95**:741 (April) 1925. Baudouin, A.; Lhermitte, J., and Lereboullet, J.: Un cas de pinéalome: Absence de macrogénitosomie précoce; le problème de la cachexie hypophysaire, Rev. neurol. **1**:388 (March) 1932. Alajouanine, T.; Hornet, T., and Thurel, R.: Pinéalome avec metastases multiples: Dissemination par le liquid cephalo-rachidien, ibid. **68**:793 (Dec.) 1937.

11. Friedman, E. D., and Plaut, A.: Tumor of the Pineal Gland (Pinealocytoma) with Meningeal and Neural Metastases, Arch. Neurol. & Psychiat. **33**:1324 (June) 1935.

tumor of the pineal body apparently extended under the ependyma of a large part of the ventricular walls, but left the ependyma itself intact.[12]

In practically all cases in which "seeding" or implantation had occurred, the pineal itself was the site of an obvious tumor, identical histologically with the secondary growths. However, it is significant for the purposes of this paper that in a few cases the pineal body has not presented such a tumor. The occurrence of so-called secondary metastases without a primary tumor is inconceivable, and suggests that the "secondary" tumors are really primary. Starck[13] reported a case of a histologically typical pinealoma in the infundibulum and floor of the third ventricle, in which the pineal body was normal in size but was surrounded by aggregations of cells identical with those in the infundibulum. Again, Globus and Silbert[14] described a large, well encapsulated pinealoma on the dorsal surface of the cerebellum. In this case the pineal body was normal in size, location and outline. Gautier, Jentzer and de Morsier[15] observed histologically characteristic pinealoma in the anterior part of the third ventricle, invading the infundibulum and optic chiasm. The site of the pineal body was occupied by a fibrous excavation, not connected with the tumor and not extending into the third ventricle. Finally, Ford and Muncie[16] reported 3 cases in which a tumor arising in the anterior part of the third ventricle had replaced practically the whole ependyma. In all 3 cases the pineal body itself was normal, although histologically the tumors resembled pinealoma. Ford and Muncie declared that the resemblance was only "superficial" and decided that the tumors could not be pinealomas, presumably because the pineal body was normal. It is customary, however, to identify tumors of the brain according to their histologic characteristics, rather than their sites of origin. The photomicrographs in Ford and Muncie's article show their cases to be closely similar to mine. In the present case, however, additional features suggest that the tumor, though histologically a pinealoma, arose not from the pineal body but from the region of the ventricular ependyma. This apparent contradiction seems to be explained by reference to the origin of the pineal body itself from the ependyma.

12. Groff, R. A.: The Dissemination of Glioma by Extension at a Distance, Am. J. Cancer **29**:651 (April) 1937.

13. Starck: Tumor der Glandula pinealis und des Hypophysisgebietes, Zentralbl. f. d. ges. Neurol. u. Psychiat. **48**:72, 1927.

14. Globus and Silbert,[1] case 4.

15. Gautier, P.; Jentzer, A., and de Morsier, G.: Syndrome infundibulaire avec atrophie optique bilatérale chez l'enfant: Pinéalome développé dans le troisième ventricule, Rev. d'oto-neuro-opht. **10**:407 (June) 1932.

16. Ford, F. R., and Muncie, W.: Malignant Tumor Within the Third Ventricle: Three Cases of Unusual Type with Invasion of the Ventricular Walls, Arch. Neurol. & Psychiat. **39**:82 (Jan.) 1938.

REPORT OF A CASE [17]

W. O. B., a white youth aged 18, was admitted to the East Moline State Hospital on Nov. 20, 1935, because of restlessness, confusion, amnesia and delirium. These symptoms had begun insidiously three years before and had progressed steadily. The diagnosis on admission was tuberculous meningitis.

General physical examination revealed no abnormalities. There was roentgenographic evidence of a healed tuberculous lesion in the apex of the right lung, but the reaction to the Mantoux test was negative and the rectal temperature

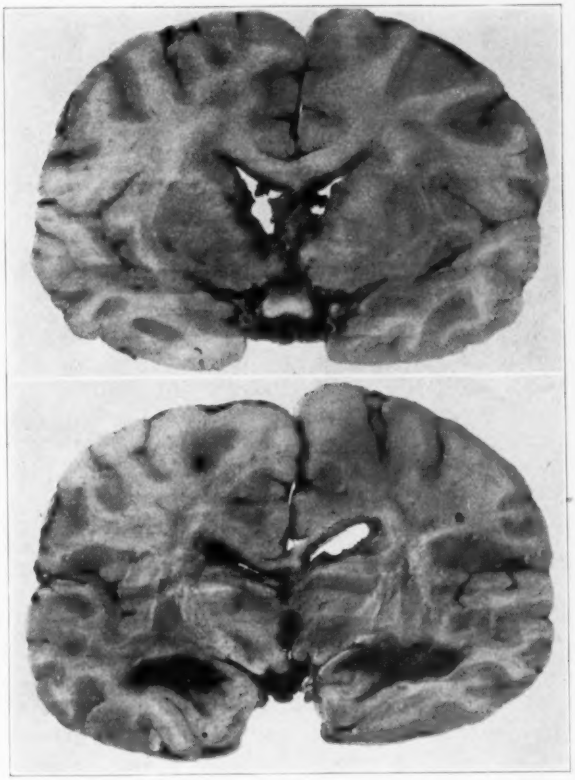

Fig. 1.—Photograph of frontal sections of the brain, showing the ependymal situation of the tumor. No normal ependyma was present anywhere in the brain.

usually subnormal (from 96.5 to 99.0 F.). The sputum contained no tubercle bacilli. The erythrocyte count was 4,260,000 per cubic millimeter; the hemoglobin 80 per cent, and the leukocyte count 6,000 per cubic millimeter, with 65 per cent polymorphonuclear leukocytes, 29 per cent lymphocytes, 5 per cent monocytes and 1 per cent eosinophilic leukocytes. Schilling hemograms showed a "shift to the left." The Wassermann reaction of the blood was negative. On neurologic examination the right pupil was larger than the left, and both were sluggish in reactions

17. The clinical data were furnished by Dr. J. A. Campbell, managing officer of the East Moline State Hospital.

to light and in accommodation. The optic fundi were normal. The patellar and achilles reflexes were equally exaggerated on the two sides; the abdominal and cremasteric reflexes were absent, and the plantar responses were normal. There was hyperesthesia over the whole body.

The spinal fluid pressure was zero; the cell count 39 per cubic millimeter; the Pandy and Ross-Jones reactions were graded as 4 plus, and the sugar content was 68.9 mg. per hundred cubic centimeters; the Wassermann and Kahn reactions were negative, and the colloidal gold curve was 1112345544. No micro-organisms were seen, and inoculation of guinea pigs gave negative results. After spinal

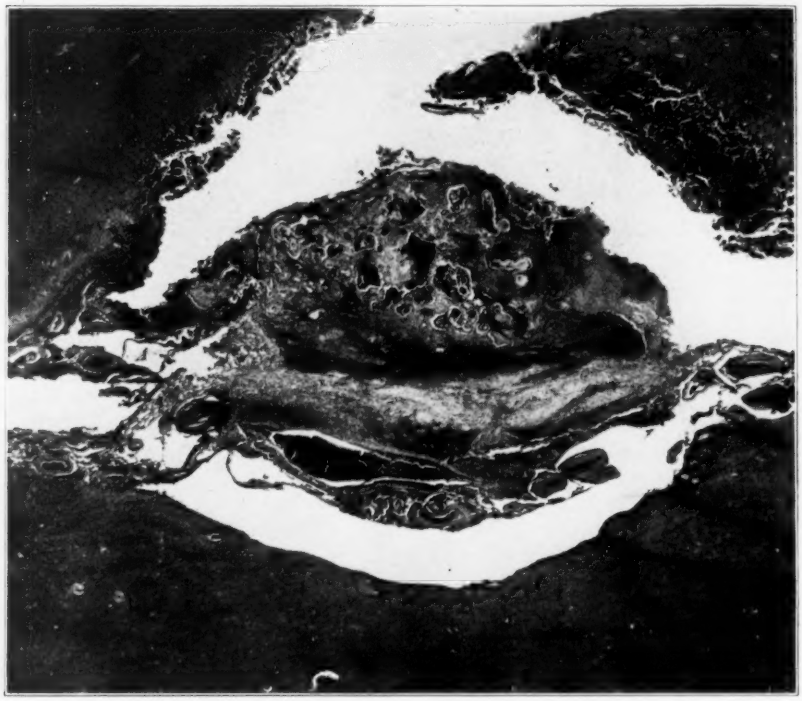

Fig. 2.—Photograph of the pineal body, which is normal in size, contains calcium concretions and is surrounded by tumor tissue. Phosphotungstic acid hematoxylin.

puncture the patient began to have rigidity of the neck, opisthotonos and a positive Kernig sign, with delirium and muscular twitches of the whole body. He died on Dec. 2, 1935, twelve days after admission.

Gross Pathologic Changes.—Autopsy revealed no abnormalities except in the brain. There was no lymphadenopathy. Externally, the brain was normal in appearance except for engorgement of the meningeal vessels. In frontal sections the entire lining of all four ventricles was seen to consist of dark brown, crumbling, granular tumor tissue, varying in thickness from 1 to 10 mm. (fig. 1). The tuber cinereum was completely packed with this tissue, and the brain substance had

been invaded for several millimeters in numerous locations. The cerebral aqueduct was completely obliterated; the choroid plexus for the most part was buried. The pineal body was normal in size and position, but the tumor tissue surrounded it (fig. 2). The ventricular fluid was blood stained and contained small particles of the tumor.

Microscopic Appearance.—The entire ependyma of the ventricles had been replaced by the histologically unique tumor. Its cells were of two types, large

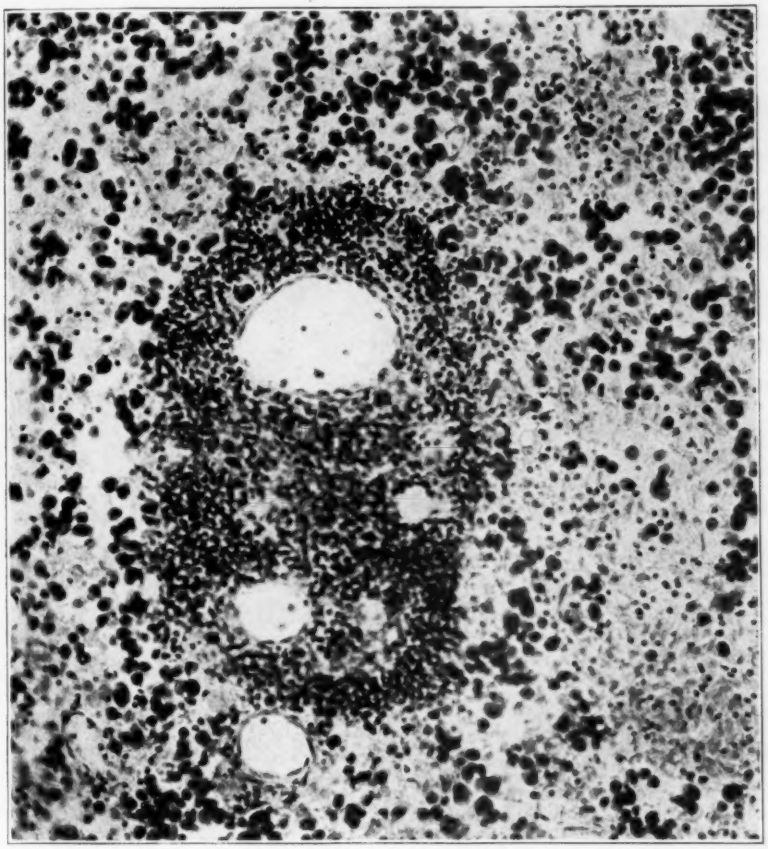

Fig. 3.—Photomicrograph of the tumor, showing the large parenchymal and smaller lymphocyte-like cells, which are scattered diffusely but are chiefly perivascular. Hematoxylin and eosin.

and small. The small cells were of the size of lymphocytes and consisted of densely staining, almost homogeneous nuclei without discernible cytoplasm. Many were scattered singly or in bands throughout the masses of large cells, but they were most common in a perivascular cuff, which varied from 1 to 10 cells in thickness (fig. 3). Perivascular accumulations of these cells were especially pronounced in the brain tissue immediately ahead of the invading tumor. The

larger cells were two or three times the size of a polymorphonuclear leukocyte (fig. 4). Some contained large, vesicular nuclei, with granules of chromatin and a prominent nucleolus. In many others a large globular, richly argentophilic, sometimes bilobed mass almost filled the nucleus. The cytoplasm was only a thin, faintly eosinophilic rim, which occasionally trailed off in a short, cone-shaped projection at one point. Mitotic figures were numerous and, in common with the larger nuclear globules, stained reddish in methyl green-pyronine preparations (fig. 5). A few cells contained double nuclei, and occasional multinucleated giant cells were seen (fig. 6). No definite blepharoplasts could be identified.

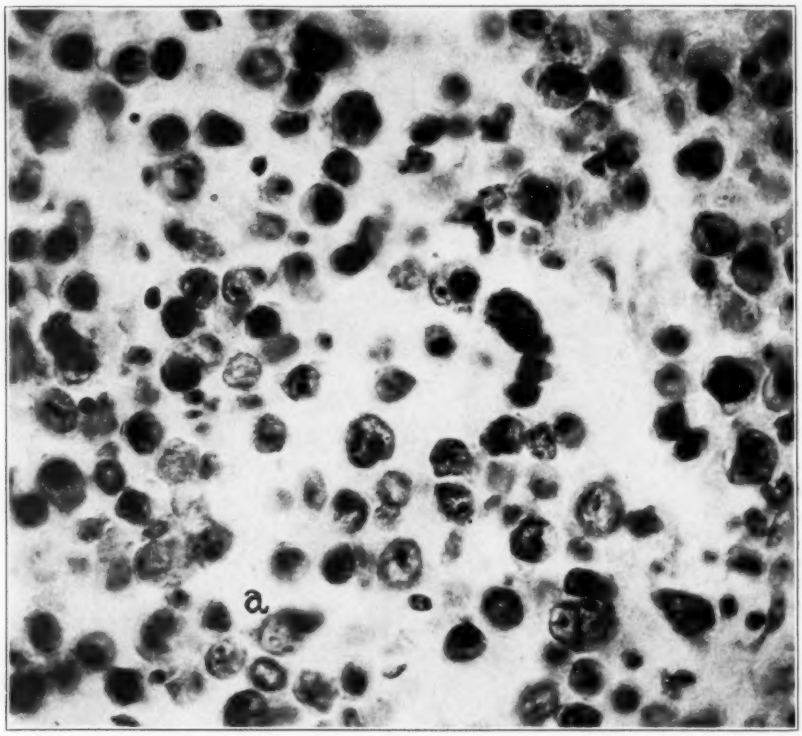

Fig. 4.—Photomicrograph of parenchymatous cells, showing some with large vesicular nuclei, prominent nucleolus and granular chromatin, and others with heavily stained intranuclear globules. One cell possesses a cone-shaped process (*a*). Some of the nuclei are multiple. Phosphotungstic acid hematoxylin.

In addition to these characteristic large and small cells, adult or immature ependymal cells appeared in numerous locations throughout the tumor. These were recognizable by their vesicular nuclei, greater amount of cytoplasm and tendency to aggregate in layers or plates or in characteristic perivascular palisades with centripetally directed vascular processes (fig. 7). When arranged in plates, these cells were flat on the side at the surface of the plate and were frequently prolonged into a tapering fibril at the other end (fig. 6). No tubules, but numer-

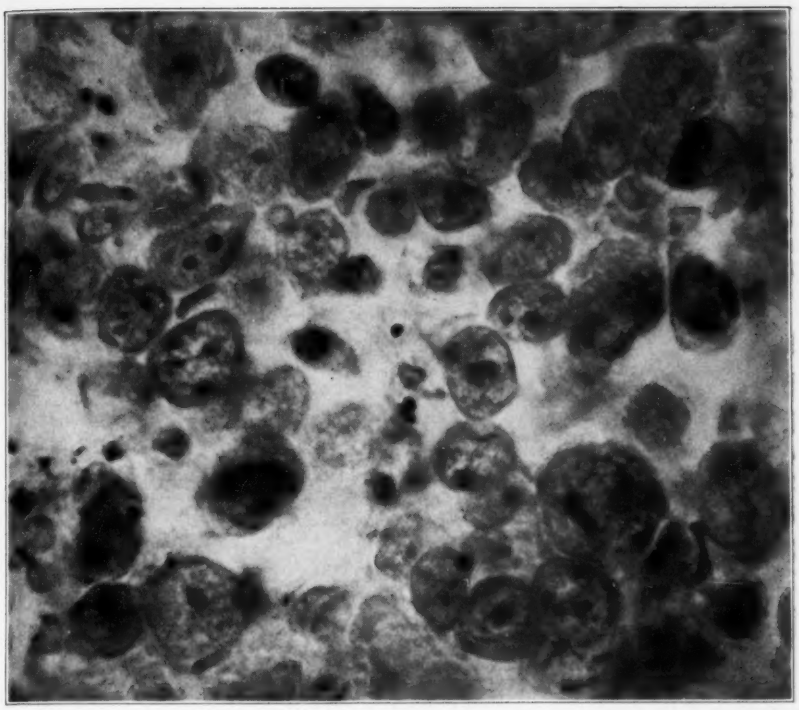

Fig. 5.—Photomicrograph showing 2 parenchymatous cells in mitosis and 1 with intranuclear globules. The chromosomes and the globules took an identically reddish stain in this preparation. Methyl green and pyronine.

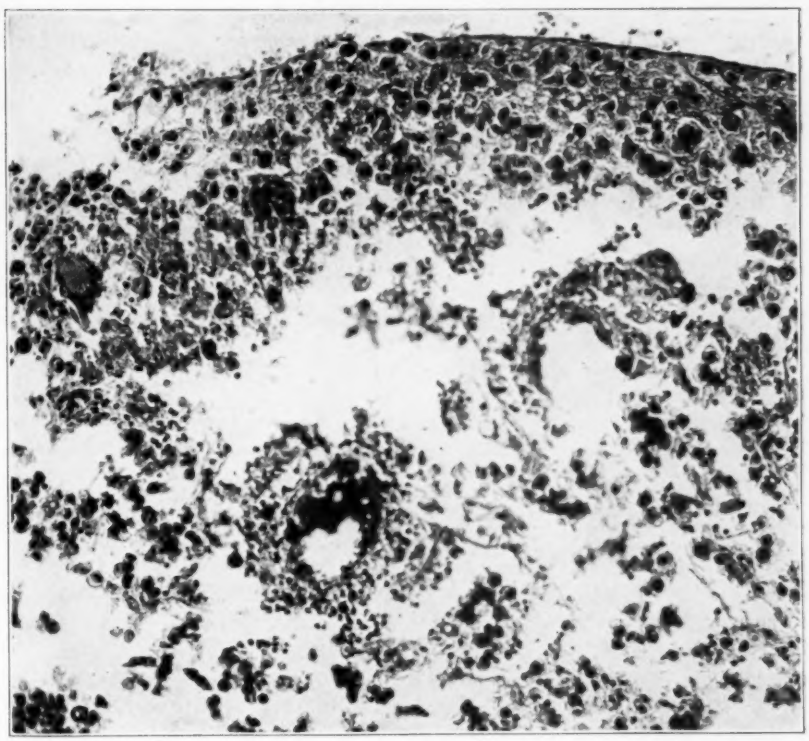

Fig. 6.—Photomicrograph showing both pineal and ependymal cells. Note the multinucleated giant cell and the fibril-bearing ependymal cells, forming an ependymal plate. Phosphotungstic acid hematoxylin.

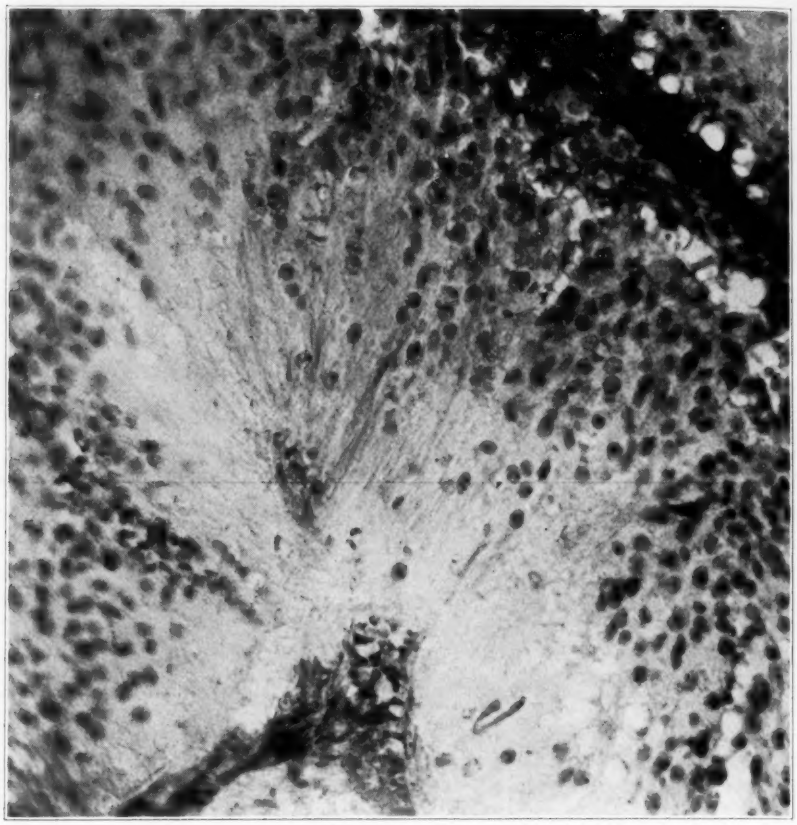

Fig. 7.—Photomicrograph of a portion of the tumor, showing perivascular palisade formation, a feature usually seen in ependymomas. Phosphotungstic acid hematoxylin.

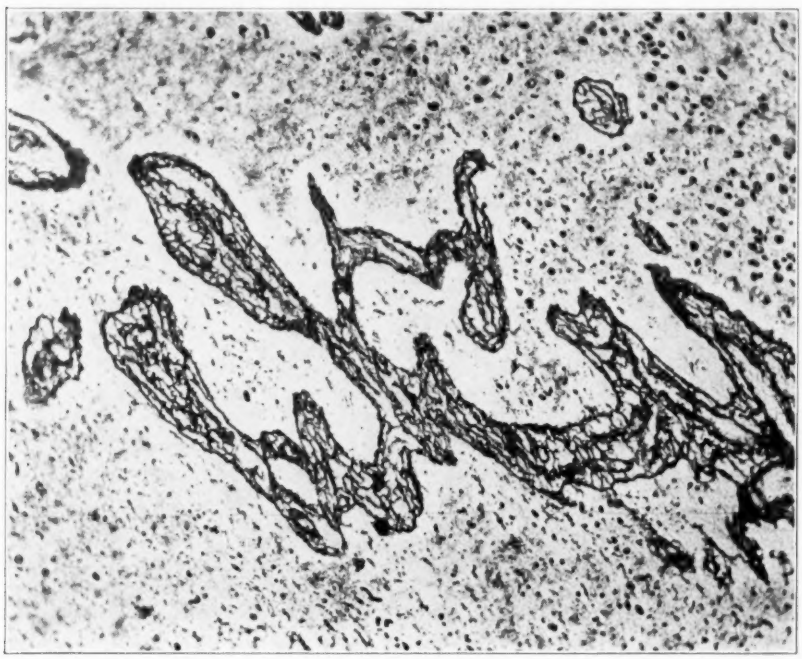

Fig. 8.—Photomicrograph of a portion of the tumor showing a reticulin network in which the smaller cells were enmeshed. Perdrau stain.

ous bipolar forms with long fibrils were seen. These spongioblastic ependymal elements and their perivascular palisades strongly suggested that they were not merely remnants of mature ependyma which had been distorted by the tumor but were in effect an integral part of the tumor formation.

The whole neoplasm was very vascular, and an extensive network of reticulin surrounded the vessels and extended throughout the tissue (fig. 8). The small lymphocyte-like cells were located chiefly in the meshes of this reticulin.

The pineal body itself was not enlarged and had produced no pressure on neighboring structures. It was surrounded by tumor cells, which tended to invade the adjacent tissues. Identical cell forms, particularly the smaller ones, were seen in the pineal body, chiefly in its periphery. The central portions had undergone considerable degeneration and fibrosis and contained many calcium concentrations (fig. 2). No definite ependymal elements could be identified in the pineal body, although a few bipolar spongioblasts were present.

COMMENT

The interpretation of this tumor is difficult. Its pinealomatous characteristics seem obvious, particularly the unique association of typical large cells with smaller units resembling lymphocytes, enmeshed in a delicate, predominantly perivascular, reticulin network. So far as I know, this morphologic picture and architecture are found nowhere but in the pinealomas.

On the other hand, it is difficult to imagine that this extensive tumor of the entire ventricular wall arose from the pineal body, which was not enlarged and which seemed to have been invaded by rather than to have given origin to the tumor. The distribution of the tumor strongly suggests an ependymal origin. Added to this is the fact that definite ependymomatous structures and cell forms were scattered throughout the tumor—blastomatous elements which could scarcely be the product of a normal ependyma invaded by another neoplasm. True, Glaser [8a] and de Busscher [8b] have seen perivascular palisades in pinealomas, but these have never been described in secondary implants, and they were not present in the pineal body in this case.

From these considerations, it seems likely that this "pinealoma" arose not from the pineal body but from the region of the ependyma. Since the pineal body is embryologically a highly differentiated ependymal structure, it is understandable that this tumor, histologically a pinealoma, may have arisen elsewhere in the ependyma, perhaps in the infundibular region, from anlages capable of producing both cell types. Such a hypothesis would explain the cases reported by Starck, Globus and Silbert and Gautier and his associates in which extrapineal pinealomas occurred. It would also account for the interesting tumors described by Ford and Muncie, which this tumor so closely resembles.

SUMMARY

A case is reported of a tumor diffusely situated in the entire cerebral ependyma. Histologically, the tumor was characteristic of the pinealomas, with the additional presence of ependymal spongioblasts and perivascular palisades. The pineal body was normal in size, outline and location, but was surrounded by the pinealomatous elements.

It is suggested that the tumor arose not from the pineal body but from anlages in the ependyma.

DISCUSSION

DR. PERCIVAL BAILEY: This tumor has the histologic structure of a pinealoma; as Dr. Mackay said, other tumors have been described having the structure of a pinealoma, although the pineal body was normal. My colleagues and I have had 1 such case recently. I think the explanation Dr. Mackay gave is correct. Some of the differences in the structure of the nuclei in his case might be due to portmortem changes. I do not know how long after death the examination was made or how the brain was fixed, but if it was immersed in solution of formaldehyde many of the nuclei undoubtedly have undergone such changes.

DR. PAUL C. BUCY: Dr. W. Muncie sent me his sections some time ago; I agree that the sections were similar to those shown here. I was impressed with the similarity between the tumor in this case and one from the hypothalamus which I have seen. The child presented only the signs and symptoms of involvement of the infundibulum and optic chiasm. At operation only a small bit of tissue was removed for examination. Its appearance was practically identical with that in Dr. Mackay's case. After operation roentgen therapy was given. The child is still alive and relatively well. Whether this is a tumor arising from the ependyma, as those of Mackay and of Ford and Muncie appear to be, or whether it represents a hypothalamic implant from an actual tumor of the pineal body (of which there is no evidence) cannot be stated.

DR. R. P. MACKAY: The statement is made that precocious sexual development does not occur in girls who have pinealomas. It is not true that pineal tumors do not occur in females, but I believe that they predominate in males.

HEMORRHAGES INTO THE CENTRAL NERVOUS SYSTEM FOLLOWING LUMBAR SPINAL PUNCTURE

SERGE ANDROP, M.D., CATONSVILLE, MD.

In reviewing the literature on hemorrhages into the central nervous system following lumbar spinal puncture, I was amazed by the paucity of cases reported, and felt somewhat like Schube and Raskin,[1] who, after a review of the literature on the subject in 1936, remarked:

> The rarer a disease, the greater is the interest in it and the less rare it becomes —due to the fact that more vigorous attempts are made to unearth cases of it. On the other hand, the rarer the unfortunate accidents accompanying a valuable and therapeutic procedure such, for instance, as the lumbar spinal puncture, the less apparent is the interest which the accidents arouse, so that practically no cases are unearthed and no attempts are made to study those which are. If one may judge the frequency with which spontaneous cerebral hemorrhage is a sequel of the lumbar spinal puncture by the number of verified cases existing in the available literature, this type of accident is certainly rare—so rare that the possibility of its existence may even be denied. It is the opinion of the writers that this type of accident is not nearly so rare as the existing literature would indicate, and that to deny that such an accident may occur is pure folly—an attitude unworthy of the medical profession.

On the other hand, if there is taken into consideration the number of lumbar spinal punctures which must have been performed since perfection of the method, the frequency of deaths due to hemorrhage into the central nervous system following lumbar puncture is extremely rare.

Besides reporting their own case, Schube and Raskin collected from the literature 14 cases of cerebral hemorrhage following lumbar spinal puncture. In 8 of the 15 cases a tumor of the brain was seen at autopsy, and in 2 cases rupture of an aneurysm. In 2 of their cases the bleeding extended into the spinal canal, and in 6 cases, into a ventricle. Riser, Planques and Becq [2] reported four cases of death after lumbar puncture, in which there was arterial hypertension. Whiteside [3] reported a case

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From the Neurological Laboratory, the Henry Phipps Psychiatric Clinic, and the Spring Grove State Hospital, Catonsville, Md.

1. Schube, P. G., and Raskin, N.: Cerebral Hemorrhages Following Lumbar Puncture, J. Nerv. & Ment. Dis. **84**:636 (Dec.) 1936.

2. Riser, Planques and Becq: Accidents graves après ponction lombaire chez des hypertendus artériels, Bull. et mém. Soc. méd. d. hôp. de Paris **54**:62 (Jan. 24) 1938.

3. Whiteside, G. W.: Lumbar Puncture; Paralysis; Death, New York State J. Med. **25**:937, 1925.

of paralysis and death following lumbar puncture. Hammes [4] reported a case of hemorrhage in the cauda equina secondary to lumbar puncture. Cooke [5] reported a similar case. His patient presented severe cerebral and spinal symptoms after a third puncture, resulting in bloody fluid, and died on the following day. Autopsy revealed a hemorrhage extending upward from the lumbar region on the left side, beneath the pia and between the nerves of the cauda equina. It measured about 8 mm. in diameter and ended at the level of the conus medullaris. Autopsy also revealed tuberculous cerebral and spinal meningitis, early bronchopneumonia and caseous tuberculosis of the left bronchial lymph nodes. For a more detailed analysis of the literature on cerebral hemorrhages which have followed and probably been caused by lumbar puncture the reader is referred to the article by Schube and Raskin.[1]

Although my primary concern is with hemorrhages into the central nervous system following lumbar spinal puncture, it is of interest to note statistical data relating to complications in general following spinal puncture. Süss,[6] of the neurologic clinic of the University of Cracow, reported such data. The material consisted of 2,913 punctures done in the clinic during eighteen years; of these 2,817 were lumbar. Complications were fatal in 10 cases, in 9 of which tumor of the brain was found. In all cases death occurred within four days after the puncture. The meningeal syndrome was the most frequent complication. He observed that lumbar punctures were followed by complications more often in adults than in children, and more often when the puncture was carried out with the patient sitting than when lying down.

REPORT OF A CASE

History.—F. B., a married man aged 55, a farmer, was admitted to the hospital on May 8, 1937, in an alcoholic stupor, and after a week of intensive hydrotherapy was discharged as improved, his family insisting on his release, contending that he was needed to look after the farm. After he had left the hospital, a positive Wassermann reaction of the blood was reported, and the patient was notified of the result and immediate treatment advised. It was later learned that he received only several intravenous injections of arsenicals. He was readmitted on May 2, 1938, this time with a "paraldehyde jag." The family history was noncontributory. Nothing was known of the patient's infancy and childhood; he had received no schooling and could neither read nor write, though he could sign his name. He had had the "usual diseases of childhood" and typhoid fever at the age of 25,

4. Hammes, E. M.: Hemorrhage in the Cauda Secondary to Lumbar Puncture, Arch. Neurol. & Psychiat. **3**:595 (May) 1920.

5. Cooke, J. V.: Hemorrhage into the Cauda Equina Following Lumbar Puncture, Proc. Path. Soc. Philadelphia **14**:104, 1911.

6. Süss, I., cited in Complications Following Spinal Punctures, Foreign Letters (Poland), J. A. M. A. **112**:348 (Jan. 28) 1939.

without any complications or sequelae. He had been a farmer throughout his life, with fair success. He had been married three times and had 2 children; the first two wives died; the present wife drank to excess.

The patient had been drinking since the age of 13, going on "week end drunks" until the age of 45; since then he had been on several protracted bouts, each lasting from one to two months, during which he consumed large amounts of alcoholic liquor. He was described as a hale, hearty, jovial, good fellow, with many friends. He said: "I have never done any harm to any one but myself, and that through drinking."

He was admitted to the hospital on the complaint of his wife that he had started on a "heavy spree" six weeks before, continuing without interruption to the time of admission. However, for a short time previous to the last alcoholic bout his behavior had been unusual; he consorted with Negroes, spent money recklessly, made unnecessary purchases, threatened to kill his wife and struck his stepson in one of many outbursts of temper.

Physical Examination.—The patient was well built but obese; he was 70½ inches (179 cm.) in height and weighed 237 pounds (107.5 Kg.). The blood pressure was 155 systolic and 95 diastolic. A healed penile scar was noted. Neurologically, there were coarse tremors of the hands, and the knee reflexes were barely elicitable. Physical and neurologic examination otherwise gave normal results.

Course.—On recovering from the alcohol-paraldehyde intoxication, the patient showed no disturbance of mood or mental content; he denied having hallucinations; the sensorium showed slight deficit, possibly in keeping with lack of education; he showed good insight into his condition in regard to drinking. In view of the positive Wassermann reaction of the blood, a spinal puncture was attempted, but the patient refused to submit because of a premonition that he would die; the family's written consent was therefore obtained. Lumbar spinal puncture was attempted at 4 p. m. on May 11, 1938, nine days after his admission, but proved unsuccessful. Three attempts at puncture, all apparently below the second lumbar vertebra, resulted in "bloody taps," and the procedure was abandoned; the patient was placed in bed. During the night he became actively disturbed, requiring the administration of paraldehyde.

I shall now quote verbatim the report of the physician performing the puncture: "The man was a huge fellow, with landmarks that were not clear. I determined the spot for the needle by drawing a line across the iliac crests, and am under the impression that the first puncture was between the third and the fourth lumbar vertebra. Frank blood, without a trace of spinal fluid, dropped from the needle. I then changed to a smaller needle and made a second and third attempt in the space immediately above, which I judged to be between the second and the third lumbar vertebra. No spinal fluid was obtained with these punctures, and only a small amount of blood, perhaps 3 or 4 drops with each one."

On the following day the patient was extremely restless and apprehensive and complained much of pain in his back and especially in the neck. He also complained of not being able to move his lower extremities. However, he walked to the bathroom with the assistance of two attendants. On May 13 he became hallucinated in both the auditory and the visual sphere; he continued to be restless,

tossing about in bed; he could not stand or walk, but was able to move his legs. Numerous hemorrhagic vesicles appeared over the calves of both legs, and there was complete analgesia of the lower half of the body, with loss of control of rectal and vesical sphincters. On May 14 he presented flaccid paralysis of

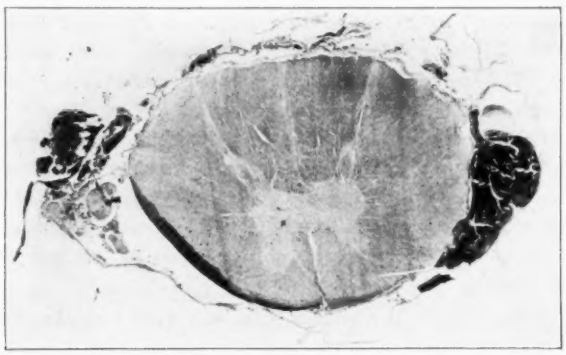

Fig. 1.—Subdural hemorrhage into the thoracic region of the spinal cord. Mahon stain.

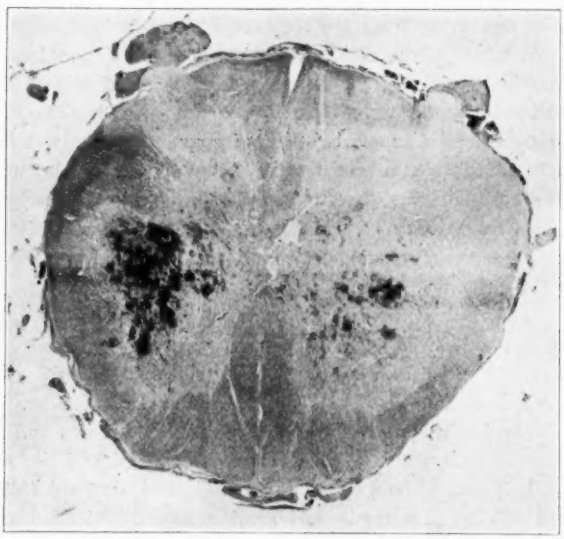

Fig. 2.—Hemorrhage into the gray matter of the lumbar region of the spinal cord. Mahon stain.

both lower extremities; the knee, ankle and plantar reflexes were absent; the abdominal reflexes were feeble, and the cremasteric reflexes were not elicited. Reflexes in the upper extremities were present; the ocular reflexes were normal; no facial asymmetry was noted; the tongue protruded in the midline; the abdomen was greatly distended. The patient continued to hallucinate and was noisy, out of

Fig. 3.—Hemorrhage into the gray matter of the lumbar region of the spinal cord. Higher magnification than that in figure 2. Mahon stain.

contact, restless and incontinent. The course of the illness was afebrile, the temperature fluctuating between 98 and 100 F. throughout the illness, reaching 100 F. only for a very brief period. On May 15, at about 3 a. m., he had a cold sweat, uttered a cry, rolled out of bed to the floor and was found to be dead.

Autopsy.—There were: (1) cirrhosis of the liver; (2) aortic insufficiency, and (3) a thin subdural hematoma of the spinal cord, extending about 3 inches (7.5 cm.) above the cauda equina. The brain and spinal cord were removed. Gross examina-

Fig. 4.—Hemorrhage into the posterior segment of the hindbrain, about the region of the nucleus of the tractus solitarius. Thionine stain.

tion revealed the following facts: The brain was within normal limits in both size and weight; the dura was normal in thickness and appearance, and stripped easily; the surface of the brain appeared normal; the convolutions were full and the sulci narrow; the superficial vessels over the lateral surfaces of the hemispheres were injected with blood and somewhat distended; the circle of Willis and other blood vessels did not show any noticeable sclerosis of the walls; the cerebral hemispheres were symmetric; the cerebellum was normal in size and shape. The brain stem and cranial nerves seemed normal. The pia-arachnoid appeared normal, and the cerebrospinal fluid was apparently normal in quantity and appearance. A succession

of vertical sections of the brain revealed no signs of hemorrhage or any other gross pathologic condition. The spinal cord contained a subdural blood clot, about 3 inches (7.5 cm.) long, involving the lumbar region and extending into the lower thoracic region. The lateral surfaces of the cord in the thoracic and lumbar regions presented several small subarachnoid ecchymoses. The meninges of the cord showed no apparent deviation from the normal. Microscopically the picture was that of an acute accident. The meninges of the cord were slightly edematous and thickened; the pia-arachnoid was composed of thickened bundles, in the meshes of which blood was present. The pial vessels were distended—some empty, others filled with blood. In the lumbar region of the cord large masses of subdural blood were seen. The gray matter of the cord at this level showed the greatest involvement. There were large hemorrhagic areas involving both halves of the cord, the anterior columns being the areas of predilection, with the central and lateral portions on a level with the gray commissure especially favored. The left side presented the most damage; the blood vessels were distended with blood, and there were large areas of perivascular hemorrhage. The red blood cells, which extended into the nerve tissue, in the areas of extravasated blood, tended to retain their original form to a great extent. There was considerable edema of the tissues, but no great amount of actual tissue destruction was seen. The edema extended into the white matter of the cord just outside the anterior columns, into the anterior and lateral funiculi, resembling to some extent the picture of status spongiosus. The posterior columns were comparatively unaffected. In the thoracic region there were several small perivascular extravasations, in much the same location as in the lumbar region. Another large hemorrhagic area was seen in the posterior segment of the hindbrain, located at about the area of the nucleus solitarius. Here, there were a large amount of extravasated blood, edema and considerable destruction of nerve tissue in the center of the lesion. Acute changes of the ganglion cells were seen in the anterior horns, but more distinctly about the hemorrhagic area in the hindbrain segment. There were no signs of any changes in the blood vessels or in their walls, of any perivascular infiltration with lymphocytes or plasma cells or any changes in the parenchyma suggestive of dementia paralytica of tabetic type or of meningovascular syphilis. There was no proliferation of neuroglia.

COMMENT

From the events preceding death and from the observations at autopsy and the neuropathologic studies, it was thought that the lumbar spinal puncture was a definite contributing factor in the production of the hemorrhages in the spinal cord and hindbrain and the resultant death within eighty-two hours. The microscopic picture of the red cells in the hemorrhagic areas of the nerve tissue, tending to retain their original form, is a reliable indication of a recent hemorrhage. It may at first appear that the size of the hemorrhage could not have been responsible for the resulting paralysis and death; however, Blake,[7] in reporting a case in which a very slight hemorrhage in the anterior horns of the cervical portion of the cord, due to an accident, resulted in paralysis of both arms, concluded that a small hemorrhage into the nervous system may produce serious results.

7. Blake, J. B.: Hemorrhage into the Spinal Cord, Internat. Clin. **28**:92, 1918.

The lengthy report of this case was prompted by the rareness of cases of this complication in the medical literature, which is too amazing to be true. In none of the cases reported in the literature is there mention of a hemorrhage into the nerve tissue of the spinal cord following spinal lumbar puncture, and little is known regarding its mechanism. Knowledge of the malignant hemorrhages due to lumbar puncture will increase as the literature about them increases, and not before.

What factors may have been present in this case which made possible the hemorrhage into the central nervous system after lumbar spinal puncture? The possibilities may be grouped under several headings: (1) vascular tumors; (2) increase in blood pressure above that which the blood vessels could withstand; (3) weakness of the blood vessels of the brain and spinal cord caused by syphilis or arsenicals or a combination of the two; (4) decrease in the pressure outside the blood vessels, by removal of cerebrospinal fluid, to such an extent that the walls were unable to withstand the pressure of the blood inside them; (5) any combination of the last three factors mentioned; (6) rupture of an aneurysm; (7) coincidental syphilitic thrombosis of a spinal artery; (8) embolism, and (9) extension from the cauda equina.

A thorough search for tumors in the brain and cord in this case proved fruitless, vascular tumors as a cause of the hemorrhage being thus ruled out. The increase in blood pressure above that which the blood vessels could withstand can also be safely ruled out, because clinically the patient showed no signs of hypertension, his blood pressure at no time reaching higher than 155 systolic and 95 diastolic. Weakness of the blood vessels of the brain and spinal cord caused by syphilis or arsenicals or a combination of the two could not seriously be considered in the present case. Clinically there were no signs of cerebrospinal syphilis, and the absence of any changes in the walls of the blood vessels or of perivascular infiltration with lymphocytes and plasma cells or of any changes in the parenchyma rules out syphilis of the central nervous system. For the same reason, coincidental syphilitic thrombosis of a spinal artery can be ruled out. Various investigators have found that syphilitic persons treated with arsphenamine show pathologic changes which they claimed were due to the arsenic; among these changes is "hemorrhagic encephalitis." Purpura of the brain with diffuse hemorrhage and edema of the meninges has been described as following the experimental injection of large doses of tryparsamide into rabbits.[1] My patient had received only several doses of arsenicals intravenously about ten months previous to the spinal puncture; therefore arsenic as a cause of weakness of the walls of the cerebral blood vessels is also ruled out. Decrease in the pressure outside the blood vessels, by removal of cerebrospinal fluid, to such an extent that the walls were unable to withstand the pressure of the blood inside them could play no part in this case, for no cerebrospinal fluid was withdrawn by any of the three punctures. Neuropathologic study revealed no signs of an embolism or ruptured aneurysm. By a systematic process of exclusion, all the probable causes of hemorrhage were eliminated but one, namely, extension of the hemorrhage from the cauda equina. This may be taken into consideration as a possible, but not plausible, cause of the hemorrhage into the posterior

segment of the hindbrain and the segments of the spinal cord, as it has been established that there is unquestionably a free communication between the perivascular spaces of the brain and cord and the subarachnoid spaces (Weed,[8] Dandy and Blackfan,[9] Cushing,[10] Ayer [11] and Fremont-Smith and Hodgson [12]).

SUMMARY

1. A brief résumé is presented of the literature on hemorrhages into the central nervous system which have followed and probably been caused by lumbar spinal puncture.

2. A case is reported in which hemorrhages into the central nervous system and death occurred after lumbar spinal puncture.

3. The possible mechanisms of the production of the hemorrhages in the case reported are formulated.

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9. Dandy, W. E., and Blackfan, H. D.: An Experimental and Clinical Study of Internal Hydrocephalus, J. A. M. A. **61**:2216 (Dec. 20) 1913; Internal Hydrocephalus: An Experimental, Clinical and Pathological Study, Am. J. Dis. Child. **8**:406 (Dec.) 1914; Internal Hydrocephalus: Second Paper, ibid. **14**:424 (Dec.) 1917.

10. Cushing, H.: Studies in Intracranial Physiology and Surgery, New York, Oxford University Press, 1925; Third Circulation and Its Channels, Lancet **2**:851 (Oct. 24) 1925.

11. Ayer, J. B.: Puncture of the Cisterna Magna, Arch. Neurol. & Psychiat. **4**:529 (Nov.) 1920; Spinal Subarachnoid Block as Determined by Combined Cistern and Lumbar Puncture, with Reference to Early Diagnosis of Cord Tumor, ibid. **7**:38 (Jan.) 1922; Cerebrospinal Fluid Pressure from the Clinical Point of View, ibid. **14**:440 (Oct.) 1925; Human Cerebrospinal Fluid, A. Research Nerv. & Ment. Dis., Proc. **4**:159, 1926.

12. Fremont-Smith, F., and Hodgson, J. S.: Combined Ventricular and Lumbar Puncture, A. Research Nerv. & Ment. Dis., Proc. **4**:172, 1926.

Technical and Occasional Notes

A CLASSROOM OUTLINE FOR THE PATHOLOGIC DIAGNOSIS OF PRIMARY INTRACRANIAL NEOPLASMS

Six Differential Characteristics

LEO ALEXANDER, M.D., BOSTON

The classification of intracranial neoplasms, since Bailey and Cushing's [1] monumental work, is based on the histogenetic principle. The scientific and practical validity of this principle is beyond doubt, but the student when confronted with the problem of making a pathologic diagnosis does not find it easy to think consistently in terms of histogenesis and by his attempt to do so may be distracted from the picture as a whole. Furthermore, the histogenetic origin of a given tumor is, in routine laboratory work, not always easy to ascertain, and in some cases, for instance in that of the neurinoma, has remained controversial, some authors considering the schwannian cells as ectodermal in origin, others as mesodermal and others classifying them as ectomesoderm (Held [2]). Therefore it has seemed advisable, in order to standardize descriptions especially for teaching purposes, to prepare an outline for classification of tumors of the brain based on purely morphologic characteristics which can easily be recognized by the student, most of them in an ordinary hematoxylin and eosin stain. These characteristics, six in number, and the diagnostic conclusions which can be drawn from each of them are summarized in the accompanying table. This table is based on the study of 180 tumors of the brain, 147 of them surgical specimens, collected in this department during the last three years.

Needless to say, the rigid framework of such a table, like every other systematization, does not do justice to the slighter variations within the material, since generally in biologic material there is some overlapping of groups and of characteristics. This is particularly true of the gliomas.

The table includes the fifteen most common types of intracranial neoplasms. The first differential characteristic, the cellular density, divides them into three distinct groups, each containing from three to seven different tumors. The second characteristic, the presence of mitoses, distinguishes eight of them. In assessing the presence and number of mitoses, however, it should be kept in mind that a peculiar degenerative change of the nuclear chromatin with formation of marginal rods, such as is found also in benign tumors and in various non-neo-

From the Neurological Unit, Boston City Hospital, and the Department of Neurology, Harvard Medical School.

1. Bailey, P., and Cushing, H.: A Classification of the Tumors of the Glioma Group on a Histogenetic Basis with a Correlated Study of Prognosis, Philadelphia, J. B. Lippincott Company, 1926. Bailey, P.: Histologic Atlas of Gliomas, Arch. Path. **4**:871-921 (Dec.) 1927.

2. Held, H.: Die Entwicklung des Nervengewebes bei den Wirbeltieren, Leipzig, B. G. Teubner, 1909, p. 87.

Outline for Pathologic Diagnosis of Primary Intracranial Neoplasms (Six Differential Characteristics)

1. Cellular density

(*a*) Very cellular with no or almost no stroma:	(*b*) Markedly cellular with some differentiation of stroma:	(*c*) Moderately cellular with a great deal of stroma:
Spongioblastoma multiforme	Astroblastoma	Protoplasmic astrocytoma
Medulloblastoma	Ependymoma	Fibrillary astrocytoma
Oligodendroglioma	Hemangioblastoma	Meningeal fibroblastoma (meningioma)
	Perithelioma	Perineural fibroblastoma (neurinoma)
	Polar spongioblastoma	Neurofibroma (von Recklinghausen)
	Neuroblastoma	
	Pinealoma	

2. Presence of mitoses:
Medulloblastoma, spongioblastoma multiforme, oligodendroglioma, pinealoma, polar spongioblastoma, perithelioma, astroblastoma, protoplasmic astrocytoma (enumerated in order of frequency)

3. Multiformity or uniformity of size and shape of nuclei (apart from mitoses)
Nuclei multiform in size and shape: Spongioblastoma multiforme
Nuclei uniform in shape (round), but of two distinct sizes (large epithelioid and small lymphoid): Pinealoma
The two types of cells in the pinealoma may be partly segregated in separate groups, partly admixed so that the individual smallest nodules may present uniformity of nuclear size

4. Determination of shape of nuclei in three subgroups of classification 1, when nuclei of tumor cells are uniform in size

Nuclei ovoid and round:		
Medulloblastoma	Certain ependymomas	Protoplasmic astrocytoma
	Astroblastoma	Fibrillary astrocytoma
	Perithelioma	
Nuclei round:		
Oligodendroglioma	Certain hemangioblastomas	
	Neuroblastoma	
	Pinealoma	
Nuclei ovoid and elongated:		
	Ependymoma	Meningeal fibroblastoma (meningioma)
	Polar spongioblastoma	Perineural fibroblastoma (neurinoma)
		Neurofibroma (von Recklinghausen)
Nuclei round, ovoid and elongated:		
	Hemangioblastoma	

5. Density of chromatin structure

Dense:		
Medulloblastoma	Polar spongioblastoma	
Spongioblastoma multiforme	Perithelioma	
	Pinealoma (lymphoid cells)	
Moderately dense:		
	Astroblastoma	Protoplasmic astrocytoma
	Ependymoma	Fibrillary astrocytoma
		Perineural fibroblastoma (neurinoma)
		Meningeal fibroblastoma (meningioma)
		Neurofibroma (von Recklinghausen)
Loose:		
Oligodendroglioma	Hemangioblastoma	Certain meningeal fibroblastomas
	Neuroblastoma	
	Pinealoma (epithelioid cells)	

6. Special differentiations

Rosette-like arrangement of cells:	Differentiation of rosettes and tubes, with or without true ependymal linings, with blepharoplasts, containing blepharoplastene granules:	Protoplasmic astrocytes (Cajal stain positive; phosphotungstic acid hematoxylin stain negative):
Medulloblastoma	Ependymoma	Protoplasmic astrocytoma
Tubelike arrangements predominating:	Perivascular arrangement of regular layers of protoplasmic astrocytes with sucker feet:	Fibrillary astrocytes (Cajal stain positive; phosphotungstic acid hematoxylin stain positive:
Neuroepithelioma, which is a subtype of medulloblastoma	Astroblastoma	Fibrillary astrocytoma
	Bipolar processes:	Whorls with differentiation of collagen and precollagen:
	Bipolar spongioblastoma	Meningeal fibroblastoma (meningioma)
	Unipolar processes:	
	Unipolar spongioblastoma	Palisades:
	Neuroblasts and ganglion cells (large light nuclei with one nucleolus):	Perineural fibroblastoma (neurinoma)
	Neuroblastoma	Axis-cylinders and collagenous fibrous tissue:
	Tumor cells lining blood-filled channels:	Neurofibroma (von Recklinghausen)
	Hemangioblastoma	

plastic, purely degenerative lesions and in such types of differentiated cells as are known never to undergo actual mitotic division, may easily be mistaken for mitoses (Porter [3]). At best, this change may be interpreted as an incomplete attempt at mitosis made by those cells, but this, of course, would be hard to prove. This change definitely does not represent mitosis in the sense of division and multiplication of cells. The third characteristic, namely, multiformity or uniformity of size and shape of nuclei, limits the diagnostic choice to one or excludes one, respectively. Nuclei of uniform shape, but of two contrasting sizes, characterize another tumor. If the nuclei are uniform in size, the determination of their shape (the fourth characteristic) divides these tumors into smaller subgroups of from one to three each. The fifth characteristic, density of chromatin structure of nuclei, allows further specification; however, it should be borne in mind that the density of the chromatin structure is of diagnostic value only in freshly fixed material and in the absence of necrosis. The sixth step consists in determining special differentiations. Of stains other than hematoxylin and eosin, the Bodian [4] stain is particularly useful in outlining the various types of glial tumor cells and their processes, especially in the tumors of group *b*. Further stains are needed for the differentiation of some of the five tumors in group *c*, namely: the phosphotungstic acid hematoxylin stain (Mallory) for fibrillary astrocytes, Mallory's connective tissue stain or Masson's trichrome stain for collagenous fibrous tissue and Bielschowsky's or Bodian's stain for axis-cylinders. Cajal's gold chloride–mercury bichloride (gold sublimate) stain is optional, since astrocytes in tumors are well stained by the methods already mentioned; however, it gives the best contrast, especially for photography.

As to the technic, I have for some time chosen the following procedure: (1) Fixation in a solution of 95 per cent alcohol (9 parts) and 40 per cent solution of formaldehyde (1 part). This solution fixes quickly and penetrates completely, avoiding irregular shrinkage. It also allows certain microchemical procedures, such as study by the microincineration method (Policard, Scott). Embedding in paraffin. (3) Cutting, preferably at 4 microns. (4) Staining: Three stains are performed routinely in all cases: hematoxylin and eosin, Masson's trichrome stain and Mallory's phosphotungstic acid hematoxylin. In many cases, additional paraffin sections are stained with the Bodian stain.

Additional blocks are fixed in a dilute solution of formaldehyde U. S. P. (1:10) or in formaldehyde and ammonium bromide for Cajal and Hortega stains; however, these fixatives are employed for purposes of research rather than for routine diagnosis.

Before study of the embedded material, a preliminary diagnosis is given during and at the various stages of the surgical operation, based on the study of smears of fresh tissue (according to Eisenhardt and Cushing [5]) or of frozen sections from tissue quickly fixed by boiling for one minute in a diluted solution of formaldehyde U. S. P. (1:10).

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3. Porter, J. E.: Personal communication to the author regarding material in preparation.

4. Bodian, D.: A New Method for Staining Nerve Fibers and Nerve Endings in Mounted Paraffin Sections, Anat. Rec. **65**:89-97, 1936.

5. Eisenhardt, L., and Cushing, H.: Diagnosis of Intracranial Tumors by Supravital Technique, Am. J. Path. **6**:541-552, 1930.

News and Comment

FELLOWSHIP AWARDS

The National Committee for Mental Hygiene announces the following appointments for one year's training in extramural psychiatry. Under a grant from the Commonwealth Fund: Dr. George E. Gardner, of the Massachusetts General Hospital, to the Judge Baker Guidance Center; Dr. John H. Waterman, of the Hastings (Nebraska) State Hospital, to the Philadelphia Child Guidance Clinic; Dr. J. Franklin Robinson, of the Iowa State Psychopathic Hospital, to the Los Angeles Child Guidance Clinic; Dr. Abraham Z. Barhash, of the Essex County (New Jersey) Mental Hygiene Clinics, to the Mental Hygiene Clinic at Louisville, Ky. Under local provision: Dr. Astor R. Schrag, of the Provincial Mental Hospital at Ponoka, Alberta, Canada, to the Detroit Children's Center; Dr. Benjamin F. Vogel, of the Psychiatric Division of Bellevue Hospital, to the Baltimore Mental Hygiene Clinic; Dr. Phyllis D. Schaefer, of the New Jersey State Hospital (Greystone Park, N. J.), to the Worcester Child Guidance Clinic.

OPPORTUNITIES FOR FELLOWSHIPS

A limited number of fellowships have been provided by the Commonwealth Fund and other sources of training in extramural, especially child, psychiatry. These fellowships are to be administered by the National Committee for Mental Hygiene, through which fellows are to be assigned for one or two years to a selected child guidance clinic, the term and plan of the fellowship to be determined by the peculiar needs of the fellows. Candidates for fellowship award should have had at least two years of psychiatry in an approved hospital for mental diseases, in addition to other qualities fitting them for extramural service. These fellowships come in response to a definite paucity of personnel in this field. Accordingly, other conditions as to age, sex and marital status must be governed by the individual case and by the nature of current demand. Requests for further information about these fellowships, and applications therefor, should be addressed to Dr. George S. Stevenson, the National Committee for Mental Hygiene, room 822, 50 West Fiftieth Street, New York.

Abstracts from Current Literature

Anatomy and Embryology

THE BLOOD VASCULAR SYSTEM OF THE HYPOPHYSIS OF AMBLYSTOMA TIGRINUM. PAUL G. ROOFE, J. Comp. Neurol. **69**:249 (Oct.) 1938.

Roofe has studied the circulation in the hypophysis in the living Amblystoma tigrinum. The blood supply to the hypophysis was seen to be from two sources, the ramus hypothalamicus and the posterior communicating artery. All parts of the hypophysis were drained by the hypothalamic vein and its immediate tributaries. In all the buccal portions except the pars tuberalis the gland cells were closely adherent to the capillaries so as to form tubules. In the pars nervosa the epithelial cells were irregularly scattered and had no constant relationship with the capillary loops. Roofe found no evidence that a second network of capillaries exists in the hypothalamic region in the venous channels from the hypophysis.

ADDISON, Philadelphia.

THE EFFERENT FIBERS OF THE THALAMUS OF MACACUS RHESUS: I. LATERAL AND VENTRAL NUCLEI. RICHARD L. CROUCH and J. KENNETH THOMPSON, J. Comp. Neurol. **69**:255 (Oct.) 1938.

To study the efferent fibers of the thalamus small lesions were produced by the Horsley-Clarke stereotaxic instrument in the ventral thalamic nuclei of 5 macaque monkeys and in the lateral thalamic nuclei of 4 others. Two weeks after the operations the animals were killed and the brains prepared by a modification of the Marchi technic. Both the lateral and the ventral nuclei were seen to send the majority of their fibers to the postcentral and precentral gyri; in addition, localized portions of these nuclei sent a few fibers to the angular, superior temporal and superior frontal gyri. Crouch and Thompson observed rich internuclear connections within the thalamus and conclude that all portions of the lateral and ventral nuclei are closely associated with the medial group of nuclei.

FRASER, Philadelphia.

PROPRIOCEPTIVE COMPONENTS OF CRANIAL NERVES. THE SPINAL ACCESSORY NERVE. KENDALL B. CORBIN and FRANK HARRISON, J. Comp. Neurol. **69**:315 (Oct.) 1938.

Thirty-eight cats were used in this investigation of the course of the proprioceptive components of the spinal accessory nerve by stimulation experiments and oscillographic studies. The isolated muscles supplied by the spinal accessory nerve were stretched manually, and the resultant action potentials were followed into the central nervous system by the cathode ray oscillograph. The physiologic findings were checked histologically by means of degeneration experiments. Corbin and Harrison found no physiologic evidence of sensory activity in that portion of the spinal accessory nerve just external to the jugular foramen, but obtained evidence of such activity as soon as it was joined by fibers from the upper cervical nerves. This evidence supports the view that whereas the motor supply of the sternocleidomastoid and trapezius muscles is through the spinal accessory nerve, the proprioceptive impulses are carried from these muscles by the spinal nerves of the upper cervical region, which accompany the peripheral distribution of the spinal accessory nerve.

ADDISON, Philadelphia.

RECIPROCAL CONNECTIONS OF THE STRIATUM AND PALLIDUM IN THE BRAIN OF PITHECUS (MACACUS) RHESUS. JAMES W. PAPEZ, J. Comp. Neurol. **69**:329 (Oct.) 1938.

Papez studied the efferent fibers of the striatum and pallidum and their relations to the composition of the basal peduncle in the brain of 2 macaque monkeys. The brains were prepared to show the Nissl substance and myelin. The efferent fibers of the striatum arose from the head and the whole length of the tail of the caudate nucleus and from the putamen. The striopallidal fibers passed from the head of the caudate nucleus and the adjoining parts of the putamen to end in the entopeduncular nucleus. Other fibers, the strionigric, continued through the pallidum and crossed the medial portion of the basis pedunculi to end in the medial portion of the substantia nigra. Fibers from the tail of the caudate nucleus ended in the pallidum and in the lateral part of the substantia nigra. Efferent fibers from the lateral and oral segments of the pallidum ended in the reticular formation caudal to the red nucleus. From the medial segment of the pallidum fibers went via the ansa lenticularis to the capsule of the red nucleus. Other fibers from the pallidum ended in the subthalamic nucleus and in the interstitial nucleus of the mesencephalon. Fibers from the subthalamic nucleus went to the lateral tegmental nucleus of the mesencephalon.

ADDISON, Philadelphia.

A PHYSIOLOGIC STUDY OF THE CEREBRAL CORTEX OF THE HAIR SEAL (PHOCA VITULINA). ORTHELLO R. LANGWORTHY, FREDERICK H. HESSER and LAWRENCE C. KOLB, J. Comp. Neurol. **69**:351 (Dec.) 1938.

Langworthy and his associates have studied the brain of the hair seal by electrical stimulation with an induction coil. Recently weaned seals were used. The motor cortex was shown to be well delimited. It lay on the ventral surface of the brain and extended almost to the tip of the frontal cortex. The body of the animal was represented upside down. On electrical stimulation all the complex movements of swimming performed by the extremities were elicited.

ADDISON, Philadelphia.

A QUANTITATIVE STUDY OF THE NEWBORN AND ADULT SPINAL CORDS OF MAN. ARTHUR M. LASSEK and GRANT L. RASMUSSEN, J. Comp. Neurol. **69**:371 (Dec.) 1938.

A quantitative study of the spinal cords of newborn infants and of adults was made by comparing measurements of the gray and the white substance of the four segments of the cord of 6 adult Negroes and 6 newborn infants. In the adult the white substance formed 82.2 per cent of the total volume of the spinal cord. In the newborn the white substance represented only 33 per cent. The thoracic region of the cord showed the greatest relative increase in length, area and volume between birth and maturity.

ADDISON, Philadelphia.

STUDIES ON THE SIZE OF THE CELLS IN THE CEREBRAL CORTEX: II. THE MOTOR AREA OF MAN, CEBUS AND CAT. GERHARDT VON BONIN, J. Comp. Neurol. **69**:381 (Dec.) 1938.

Von Bonin reports by means of frequency curves measurements of the nuclear volume of ordinary cells and of Betz cells from the motor area of man, the cebus monkey and the cat. The distribution of the Betz cells was normal; that of the ordinary cells was skewed and leptokurtic. Of the three forms examined, the ratio of the size of the Betz cells to that of the ordinary cells was greatest in man. Von Bonin suggests that the more complex the brain the greater the variability in size of its cortical cells.

FRASER, Philadelphia.

QUANTITATIVE STUDIES ON NERVE REGENERATION IN AMPHIBIA: I. FACTORS CONTROLLING NERVE REGENERATION IN ADULT LIMBS. RAYMOND LITWILLER, J. Comp. Neurol. **69**:427 (Dec.) 1938.

For this study of factors controlling nerve regeneration the adult Japanese newt, Triturus pyrrhogaster, was used. The control operation consisted of transecting the brachial nerves to the anterior limb. In the experimental operations transection was accompanied by removal of peripheral nerve trunks, by reduction of the nerve supply to the limb or by both removal and reduction of the nerve supply. One hundred and twenty days after the operation the limbs on which operation had been performed and the intact control limbs from the opposite side were treated by the Bielschowsky silver technic and the nerve fibers counted. When the nerve trunk was removed from the limb, the number of nerve fibers which grew into the limb was about three-fifths that which grew into the limbs with the nerve supply transected. Therefore Litwiller concludes that the controlling factor cannot reside solely in old nerve sheaths.

FRASER, Philadelphia.

TERMINATION OF THE BRACHIUM CONJUNCTIVUM IN THE THALAMUS OF THE MACAQUE MONKEY. RICHARD L. CROUCH and J. KENNETH THOMPSON, J. Comp. Neurol. **69**:449 (Dec.) 1938.

Lesions were produced in the brachium conjunctivum of 2 monkeys. The brains were stained with the Marchi technic, and the ascending course of the fibers was studied. Fibers were traced to the red nucleus and to the nucleus ventralis intermedius of the thalamus.

ADDISON, Philadelphia.

THE THALAMUS OF THE CHIMPANZEE: II. ITS NUCLEAR STRUCTURE, NORMAL AND FOLLOWING HEMIDECORTICATION. A. EARL WALKER, J. Comp. Neurol. **69**:487 (Dec.) 1938.

Walker studied the nuclear structure of the thalamus of the anthropoid ape, Pan satyrus, from a normal animal and from an animal two months after removal of the cortex from one hemisphere, except for the inferior surface of the frontal and temporal lobes. The thalamus of the chimpanzee is larger both absolutely and relatively than that of the macaque monkey, but is smaller than that of man. After hemidecortication there was almost complete degeneration of the following nuclei: anteroventralis; ventralis posterior; ventralis lateralis; lateralis posterior; lateralis dorsalis, and medialis dorsalis, and of the lateral and medial geniculate bodies. Walker compares his observations with those of other authors who have described the thalamus of lower mammals after hemidecortication.

ADDISON, Philadelphia.

THE DEVELOPMENT AND INNERVATION OF TRANSPLANTED LIMB PRIMORDIA OF CHICK EMBRYOS. VIKTOR HAMBURGER, J. Exper. Zoöl. **80**:347 (April) 1939.

Wing and hindlimb primordia of chick embryos (24 to 45 somites) were transplanted to the flank or into the celom of hosts of the same stages. In 25 per cent of the cases the transplants differentiated into normal limbs, of normal or subnormal size. Small buds gave normal transplants, but medium and large buds usually formed atypical outgrowths. Study of the innervation of 32 transplants showed that those located dorsally near the spinal cord were well innervated, while those located ventrally or in the celom were poorly innervated or nerveless. The ingrowing nerves were derived from limb nerves or from trunk nerves of the host or from both, and formed a plexus before entering the transplant. There was evidence that "attractive" forces guided the nerves toward the transplant. The nerve pattern within the transplant was normal in most cases, and must have been determined by factors intrinsic in the differentiating limb. Nerves of which the peripheral area was increased showed definite

hyperplasia. Spontaneous and reactive motility was observed in a number of cases. Nerveless and poorly innervated limbs developed normally. The similarity of the results to those in experiments on amphibian embryos is pointed out.

WYMAN, Boston.

THE CAPACITY FOR DIFFERENTIATION OF FISH EMBRYONIC TISSUES IMPLANTED INTO AMPHIBIAN EMBRYOS. JANE M. OPPENHEIMER, J. Exper. Zoöl. **80**:391 (April) 1939.

Parts of teleostean embryos (Epiplatys fasciolatus) were implanted into the blastocele or into the head or tail bud of amphibian embryos (Amblystoma punctatum or Triturus torosus). By grafting the head, trunk, tail or isolated organs it was shown that the following fish structures can advance in differentiation after implantation into amphibian hosts: intestine, liver, notochord, cartilage, striated and cardiac muscle, fin, epidermis, spinal cord, brain, ear and eye. Fish epidermis and cartilage were observed to be morphologically continuous with comparable structures formed by amphibian cells. Occasionally fish grafts seemed to be innervated by nerves derived from the amphibian cranial ganglia. It was concluded that there is no specific antagonism or incompatibility between fish and amphibian tissues at the stage involved in the experiments, and that final degeneration of the grafts was due primarily to the fact that they were never vascularized by the host.

WYMAN, Boston.

Physiology and Biochemistry

THE ACTION OF CERTAIN DRUGS ON THE INSECT CENTRAL NERVOUS SYSTEM. K. D. ROEDER, Biol. Bull. **76**:183, 1939.

Solutions of various drugs were injected into the heads of adult praying mantids and cockroaches, and the changes in general reflex activity were recorded. Strychnine caused a decrease in reflex activity in both insects, large doses causing complete cessation of movements of the antennae and mouth parts. Pilocarpine and physostigmine brought about an increase in movements of the mouth parts, antennae and head and in extensor leg tonus, and produced spasmodic twitching and general contraction of the body musculature. Acetylcholine alone had no detectable effect on activity. It is concluded that, in their reactions to drugs, the nervous systems of the two insects studied show little similarity to the vertebrate central nervous system, but considerable similarity to the vertebrate parasympathetic system.

COBB, Boston.

CEREBRAL MECHANISMS. JAMES W. PAPEZ, J. Nerv. & Ment. Dis. **89**:145 (Feb.) 1939.

Papez contributes a general survey of cerebral function, in which he distinguishes three great mechanisms involving three cortical regions and the subcortical structures with which they are connected. The first of these mechanisms involves the sensory cortex of the parietal, occipital and temporal lobes, which receives afferent impulses through the ventral and lateral thalamic nuclei from receptors all over the body. Into this functional structure flows a stream of diverse and specific sensory excitations underlying perception. The second mechanism involves the prefrontal regions, which receive ill defined relays through the medial nuclei of the thalamus from the midbrain and the afferent systems in general. This region of the frontal lobe and its connected thalamic nuclei constitute a special receptive field the dynamics of which bear an organizational relation to those of the sensorium. Thus are served global functions dealing with orientation, organization, comprehension and elaborative thinking, in which the medial thalamic nuclei are as important as the cortex. In the third mechanism Papez includes the medial cortex, especially the gyrus cinguli, which is closely

connected through the anterior thalamic nuclei with the hypothalamic and subthalamic nuclei and serves to mediate general consciousness and emotional experiences. Emphasis is laid on the derangements of emotional expression and experiences, of personal traits and behavior, produced by lesions in the walls of the third ventricle and in the hypothalamus. Such derangements are mental fatigue, emotional indifference, manic and schizophrenic states, apathy, somnolence and lethargy. The author insists, however, that these subcortical structures do not function in emotional life independently of the cortex, with which they are in close connection through the terminal stria from the amygdala, the medial forebrain bundle from the olfactory centers and the fornix from the hippocampus.

Papez believes that the cerebral cortex functions as a whole, but that there is a systematic and orderly organization of afferent and efferent impulses. The three receptive regions of the cortex which he discusses, viz., the posterior or sensory areas, the frontal lobes and the gyrus cinguli, appear to him to be the recipients of three differently organized excitation streams, representing the sensory, the global and the emotive processes, respectively. The concept of mass action in cerebral function implies that these must be combined in the cortex to yield integral psychologic functions. Finally, "the cortex is not an independent level of activity, but has recurrent relations to all the lower levels of the central nervous system."

MACKAY, Chicago.

THE CENTRAL PATHWAY IN MAN OF THE VASOMOTOR RESPONSE TO PAIN. D. G. MARQUIS and D. J. WILLIAMS, Brain **61**:203, 1938.

Marquis and Williams studied vasoconstrictor responses in a series of patients with lesions of the nervous system at various levels extending from the peripheral nerves to the cortex, in order to determine the anatomic pathway of these responses. The patients all had marked sensory changes, consisting of either a decrease or an increase in the intensity of the subjective appreciation of peripheral stimulation. Five normal persons and 15 patients with discrete lesions of the nervous system involving the sensory pathway were studied. It was found that in normal subjects the vasoconstrictor responses to stimuli of equal intensity on symmetric areas of the skin were equal and that they varied directly with the intensity of the stimulus. In 10 subjects with lesions of the sensory pathway below the level of the thalamus the vasomotor response varied directly with the change in the subjective appreciation of the stimuli, while in 5 subjects with lesions of the sensory tracts in the thalamus or cerebrum there was no effect on the magnitude of the vasoconstrictor response. The evidence presented suggests that in man the ascending pathway for the vasomotor response to somatic stimulation is the spinothalamic tract, and that the vasomotor reflex arc is complete in the brain stem below the level of the sensory thalamus.

SALL, Philadelphia.

VASOMOTOR CONTROL OF CEREBRAL VESSELS. H. S. FORBES and S. COBB, Brain **61**:221, 1938.

Recent experiments have clarified the confusion regarding the regulation of blood flow within the brain and its meninges. Today there is substantial agreement on several points: Intracerebral regulation exists; in this regulation chemical agents, especially carbon dioxide, play a major part; cerebral vasoconstrictor nerves are present, but they are only about one-tenth as effective in the pia as are the vasoconstrictor nerves in the skin; vasoconstrictor nerves are distributed unequally to different parts of the brain. Evidence has been obtained also for the existence of cerebral vasodilator nerves. With so many regulatory mechanisms one might expect frequent changes in the caliber of the vessels and in blood flow, even under resting conditions. Such changes do not occur normally. The capillaries, at least in the pia, appear to be always open; the arterioles do not change in size appreciably, and the flow is remarkable for its steadiness.

SALL, Philadelphia.

BRAIN POTENTIAL CHANGES IN MAN INDUCED BY METRAZOL. M. A. RUBIN and C. WALL, J. Neurol. & Psychiat. **2**:107 (April) 1939.

Rubin and Wall recorded the brain potentials of 11 schizophrenic patients given 28 injections of metrazol. The records were started five minutes before the injection and were continued up to one hour in some instances. Characteristic alterations of the electroencephalogram were observed when metrazol evoked an emotional response or a seizure. When neither of these reactions occurred there were no changes in the electrical activity of any of the major regions of the cerebral cortex. The cortical response to metrazol may be divided into three types. 1. The alpha (10 per second) rhythm was slowed to about 6 per second when only a mild emotional reaction, usually appearing as a momentary look of apprehension, was induced by metrazol. 2. As a rule the electrical activity only of the frontal lobes was appreciably altered during a severe emotional episode. The time for complete reestablishment of the premetrazol electroencephalogram was directly proportional to the severity of the emotional response; the more severe the response, the longer the time of recovery. 3. During a metrazol seizure large (250 microvolts) waves appeared from six to twenty seconds after the injection of metrazol, marking the first myoclonic stage, and continued for from three to ten seconds. During the tonic stage, which occurred from fifteen to thirty seconds after injection and lasted from ten to thirty seconds, the electroencephalogram was characterized by high voltage spikes which had the frequency of muscle potentials. The second clonic phase occurred from thirty to fifty seconds after the injection of metrazol, lasted from twenty-five to forty seconds and was associated with cortical potentials with a frequency of 3 to 4 per second and an amplitude of 1,000 microvolts; they became slower, decreased in voltage and appeared with a spike component toward the end of the seizure. Immediately on cessation of the convulsions, at which time the patient might exhibit severe emotional symptoms, the amplitude of the potential changes dropped markedly and the pattern was one of even slower, but more irregular, activity for the next five to ten minutes. The final phase, lasting until the patient was fully recovered, consisted of an increase in frequency and a dropping out of the irregular, slow waves. This last phase exhibited two of the properties of the electroencephalogram during sleep: (1) The predominant activity shifted back and forth from a level of almost complete recovery to one resembling the stage immediately following the seizure, and (2) as early as ten to fifteen minutes before the patient opened his eyes and spoke spontaneously he responded to requests by speech or by movement. The electroencephalogram reverted to the premetrazol level while the patient was responding to the request. Immediately after this the "drowsy" potential pattern typical of this phase reappeared. These two changes correspond to the shifts in the level of the cortical activity during sleep which occur spontaneously and on arousing the attention of a sleeping subject. J. A. M. A.

A CLINICAL STUDY OF THE EFFECTS OF SHORT PERIODS OF SEVERE ANOXIA, WITH SPECIAL REFERENCE TO THE MECHANISM OF ACTION OF CARDIAZOL "SHOCK." RUSSELL FRASER and FRANCIS REITMANN, J. Neurol. & Psychiat. **2**:125 (April) 1939.

To test the validity of the theory that cerebral anoxia is responsible for the clinical effects of metrazol therapy, Fraser and Reitmann investigated the effects of short periods of severe anoxia in 4 schizophrenic patients. This was induced by means of a mask from a gas anesthesia apparatus adjusted to deliver 3.5 per cent oxygen in nitrogen for two minutes, followed by 2 per cent oxygen for about three minutes. The clinical effects obtained occurred in two stages: (1) an initial stage of unconsciousness associated with various spontaneous movements, myoclonic twitchings and a continuous rise in pulse rate, respiratory rate and blood pressure; (2) stage of extensor hypertonus accompanied by a steady rise in blood pressure,

with no change in the pulse and respiration rates. With the removal of the mask, the waking stage set in rapidly, with only mild after-effects for about five minutes. The prolongation of unusual symptoms during the waking phase indicated severe exposure, reminiscent of the delayed recovery from a severe metrazol seizure or "irreversible" insulin coma. No clinical benefit was observed in these cases, and there was no evidence of permanent sequelae, such as mental deterioration. The most significant difference between the clinical effects of anoxia and those of metrazol lay in the absence of epileptiform fits in the former. The spontaneous movements were also less severe and frequent, and the vascular effects subsided more rapidly. The disturbances in tone produced by anoxia are observed only during recovery from metrazol fits. The authors conclude that metrazol produces other important changes which cannot be accounted for by anoxia, and that anoxia, although playing a part in the pathogenesis of metrazol effects, cannot be regarded as the most important mechanism. MALAMUD, Ann Arbor, Mich.

AN UNUSUAL CASE OF THE GRASP REFLEX, WITH SOME OBSERVATIONS ON THE VOLITIONAL AND REFLEX COMPONENTS. A. M. STEWART-WALLACE, J. Neurol. & Psychiat. **2**:149 (April) 1939.

Stewart-Wallace reports a case to prove that analysis of the phenomena included in the "grasp reflex" into volitional and reflex components can be made. The patient had mild right hemiplegia for fourteen years after the removal of a meningioma from the left frontal region, associated with well marked grasping movements. Four months prior to the patient's coming under observation, after a seizure, the right arm became so severely hemiplegic that voluntary groping and grasping were no longer possible, but involuntary closure of the hand could be obtained with both tactile and proprioceptive stimuli. This was demonstrated by induction of procaine anesthesia, which abolished the tactile response, but the involuntary grasp reflex could still be obtained by pressing on the surrounding muscles or stretching the flexor tendons. Accentuation of this phenomenon was produced by attempting to withdraw an object from the palm, which thus maintained the reflex action by tactile and proprioceptive stimuli.

MALAMUD, Ann Arbor, Mich.

HIGH-FREQUENCY DISCHARGE FROM CEREBRAL NEURONES. E. D. ADRIAN and G. MORUZZI, J. Physiol. **95**:27P, 1939.

The authors recorded simultaneously the potential waves from the cerebral cortex and the axon potentials from individual fibers in the pyramidal tracts. They observed that small bursts of impulses occurred in the fibers of the pyramidal tract simultaneously with the potential waves recorded from the surface of the cortex. The number of impulses in each group in the pyramidal fibers was normally 2 or 3, but was increased to 50 or more by the action of strychnine or electrical stimulation of the cortex. These impulses occurred at a very high frequency—200 to 1,000 per second—and this the authors believe may account for the ease with which impulses traveling over the pyramidal tracts overcome synaptic resistance in the spinal cord and facilitate spinal reflexes. THOMAS, Philadelphia.

BLOOD-SUGAR VARIATIONS IN NORMAL AND IN SYMPATHECTOMIZED DOGS. L. BROUHA, W. B. CANNON and D. B. DILL, J. Physiol. **95**:431, 1939.

The authors studied the regulation of blood sugar in dogs after complete sympathectomy combined with denervation or removal of the adrenal glands. They found that the animals subjected to operation were able to regulate the blood sugar within normal limits during and after exercise, after ingestion of dextrose and after injection of epinephrine, provided adequate time was allowed for recovery from the operation. However, these animals were permanently hyper-

sensitive to insulin. The latter abnormality proved to be dependent solely on the denervation or removal of the adrenal glands, since dogs deprived of the adrenal medulla were as sensitive to insulin as totally sympathectomized dogs.

THOMAS, Philadelphia.

VOLUNTARY AND INVOLUNTARY CONDITIONED RESPONSES. G. DE MONTPELLIER and J. COLLE, Arch. de psychol. **27**:134, 1939.

Seventy-four adult subjects were used in a comparative study of the conditioning of the psychogalvanic response and of the motor response of hand withdrawal under five different experimental conditions. The unconditioned stimulus in both cases was an electric shock to the finger. The conditioned stimulus was the sound of an electromagnetic vibrator. The results demonstrate that conditioning of the motor response is much less distinct than that of the psychogalvanic response, the latter occurring in 97 per cent of the tests whereas the former occurred in 68 per cent. Extinction is more rapid in case of the motor response. Comparison of results under the different experimental conditions, in so far as the motor response is concerned, shows: (1) Successive presentation of the stimuli is better than simultaneous presentation; (2) the introduction of a second task (learning of word-letter associations) during the presentation of stimuli or during test trials has no favorable effect on the conditioning process; (3) when verbal conditioning is substituted for the habitual conditioning process, the psychogalvanic response is conditioned more easily than the motor response. Finally, it is concluded that observed differences between the conditioning of the two responses seem not to be due to an inhibitory influence exerted by higher processes but to be caused by differences in the thresholds of excitation, the threshold value being less in the case of the psychogalvanic response than in that of the motor response.

SCHAEFFER, Philadelphia.

DOMINANCE OF THE MENTAL OVER THE PHYSICAL ORGANISM: I. THE REACTION OF OPENING THE EYES. A. REY and P. A. OSTERRIETH, Arch. de psychol. **27**:157, 1939.

The present investigation is concerned with the relation between a developmental factor (chronologic age) and the ability to maintain closure of the eyelids during sensory (auditory and tactile) stimulation and during intellectual activity (conversation, counting, simple mental arithmetic). One hundred and nineteen normal subjects, ranging from children 4 years of age to adults, were used. The total percentage of opening reactions ranged from 37.5 of the trials in children between 4 and 6 years to 0.8 in adults. The opening reaction was more frequent during intellectual activity than during sensory stimulation throughout the age range. In subjects under 8 years the percentages of reactions were greater during mental work than during conversation. In those above 8 years this situation was reversed. It is concluded that: (1) Dominance of the mental over the physical organism increases with age; (2) the degree of dominance furnishes a gross criterion of the degree of development; (3) if a subject between 4 and 10 years of age does not present a single opening reaction during the examination, one may conclude that a satisfactory dominance of the mental over the physical organism exists.

SCHAEFFER, Philadelphia.

A TONIC PHENOMENON IN THE PIGEON AFFECTED WITH BERIBERI. S. GETZOWA and L. HALPERN, Encéphale **2**:157, 1938.

Pigeons were fed exclusively on polished rice. After ten to twenty days the majority showed typical opisthotonos. With light touch on the front of the pigeon's neck the opisthotonos could be made to disappear. The bird seemed relieved and remained quietly on the observer's hand. As soon as the light con-

tact ended the pigeon resumed the opisthotonic posture, together with the usual violent attempts to maintain its equilibrium, such as beating its wings. This inhibition of a muscular spasm by a sensory stimulus in the region of the antagonistic musculature is compared with the antagonistic gesture in cases of spasmodic torticollis in man and in some cases of tic, paralysis agitans and athetosis. The existence of an antagonistic gesture is not evidence of the psychogenic origin of torticollis.

LIBER, New York.

EFFECT OF VEGETATIVE NERVOUS SYSTEM ON VITAMIN C CONTENT OF THE PLASMA. G. VON LUDÁNY, Arch. f. d. ges. Physiol. **241**:263, 1938.

Experiments on dogs showed that asphyxia increases the ascorbic acid in the plasma, the average increase being 50.4 per cent. This increase persists for about forty-five minutes after the asphyxia. Since asphyxia increases the state of excitation of the sympathetic system, the effects of epinephrine and of stimulation of the splanchnic nerve were studied. Both increase the ascorbic acid in the plasma. Since ascorbic acid plays an important role in metabolism and inhibits the disintegration of epinephrine, the author offers the theory that the increase of ascorbic acid on sympathetic stimulation serves an "emergency function."

SPIEGEL, Philadelphia.

STIMULATION OF VAGUS AND AORTIC NERVES IN RABBITS WITH SINUSOIDAL CURRENTS OF LOW FREQUENCY. H. MIES and H. J. MÜSCH, Arch. f. d. ges. Physiol. **241**:272, 1938.

In experiments on rabbits it was found that the optimum frequency for stimulation of the vagus nerve and the nervus depressor aortae was 25 cycles per second. The threshold of the vagus nerve was decreased by section of the vagi and also by elimination of the depressor nerves of the aorta and of the carotid sinus nerves, so that weaker currents and lower frequencies produced a negative chronotropic effect. The depressor effect of stimulation of the nervus depressor aortae could be increased by section of these nerves and of the carotid sinus nerves. Stimulation of the intact vagus nerve with a frequency of 2.5 cycles per second or below produced tachycardia, in case of the weakest currents; stronger currents induced bradycardia. Stimulation of the intact vagus nerve with very slow currents (up to 0.5 cycle per second) produced slowing of respiration, while more rapid currents always produced acceleration of respiration. Stimulation of the depressor nerve of the aorta first produced a fall of blood pressure, then, on increase of the stimulus, bradycardia and slowing of respiration; on stimulation of this nerve with currents of the lowest frequencies periodic changes in blood pressure in the rhythm of the sinusoidal current were observed. The differences of response depending on the frequency of the stimulating current were probably due to the fact that various end organs have different summation abilities, the sympathetic endings being capable of summation at low frequencies, the parasympathetic endings only at high frequencies.

SPIEGEL, Philadelphia.

SELECTIVE STIMULATION OF VEGETATIVE NERVE FIBERS IN THE FROG'S SCIATIC NERVE. A. BREITBACH and H. J. MÜSCH, Arch. f. d. ges. Physiol. **241**:360, 1938.

In the Laewen-Trendelenburg preparation of the vessels of the frog, the sciatic nerve was stimulated with sinusoidal currents of low frequency (10 to 0.1 cycles per second) in order to stimulate vasomotor fibers without stimulation of motor fibers. Selective stimulation of vasoconstrictor fibers with frequencies below 2 per second was possible; selective vasodilatation could not be obtained.

SPIEGEL, Philadelphia.

VITAMIN C CONTENT OF HUMAN BRAIN, WITH SPECIAL REFERENCE TO VEGETATIVE CENTERS. F. DIEHL and H. NEUMANN, Klin. Wchnschr. **18**:418 (March 25) 1939.

Diehl and Neumann report on the use of methylthionine chloride (as applied by Bonsignore and Martini) to determine the vitamin C content of the various portions of the brain of 19 adults, between the ages of 21 and 84, and of 1 infant, aged 7 weeks. Clinical research emphasized the difference between the vegetative and the nonvegetative brain centers. The anatomic procedure is indicated for the portions of the brain studied. The greatest vitamin C content was found in the tuber cinereum, the medulla oblongata and the hypophysis, in the order given; the lowest in the cerebellum, the corpus callosum and the cerebrum, ascorbic acid being represented by the extremes of 1.2 and 30.5 mg. per hundred cubic centimeters in the adult brains and of 48 mg. per hundred cubic centimeters in the hypophysis of the infant brain. The authors suggest that the difference in vitamin C content between the group with high and that with low values is due to the difference in vegetative centers, Bodechtel's investigations having already established the vegetative significance of the portions of the brain rich in vitamin C. On the other hand, according to the authors, the portions of the brain with the lowest content clearly have little to do with vegetative functions. Results relative to the hypophysis invite the conjecture that this structure in healthy persons contains the highest proportion of vitamin C, but that whenever a deficiency of this vitamin occurs in a person the hypophysis suffers a much earlier and more incisive curtailment of its functions. The interpretation of the results follows the conclusions of Tonutti that a high vitamin C content of an organ is indicative not of a process of "storing" vitamin energy but of the immediate active demands made by the system on it. The more active an organ is the more vitamin C it contains. The portions of the brain that are the last to cease functioning are connected with the vegetative centers and, as the most active, are richly supplied with vitamin C. This interpretation, the authors believe, also accounts for the fact that the portions of the brain intermediate between the group with high and that with low vitamin C content show so great a fluctuation. Manifestly, shortly before life becomes extinct and varying according to the person and the pathophysiologic picture, some of the intermediate portions of the brain flicker into a final intensity of function at one time or another. On the other hand, the lowest of these portions in the authors' rating scale, the cerebrum, reduces its functioning to a minimum long before death. The conclusions of others pertaining to the relations existing between age level and vitamin C content have been confirmed in this investigation.

J. A. M. A.

EFFECT OF CIRCUMSCRIBED LESIONS OF THE CENTRAL CONVOLUTIONS ON MUSCLE TONUS AND REFLEXES IN MAN. K. VON SÁNTHA, Monatschr. f. Psychiat. u. Neurol. **100**:241 (Nov.) 1938.

There is still disagreement concerning the neurologic effects of circumscribed lesions of the central convolutions. In an attempt to throw light on this problem, von Sántha made preoperative and postoperative observations in 11 cases in which such lesions were removed. The pathologic conditions consisted of meningeal-cerebral scars of traumatic or vascular origin in 9 cases, a tumor in 1 case and an aneurysm in another. In patients with single lesions confined to the premotor area (area 6 of Brodmann), the objective neurologic findings were largely normal before operation and remained normal afterward, except for transient disturbances; Leri's sign and Mayer's reflex were unchanged or hyperactive, and exaggeration of tendon reflexes, alterations of the superficial reflexes or increase of tonus did not occur. The removal of a portion of the motor area (area 4 of Brodmann) produced flaccid paralysis immediately after the operation, but within a few days or weeks this was supplanted by a spastic condition with exaggeration of the deep reflexes and diminution or absence of the superficial reflexes. When the center

for the hand was excised, Leri's sign and Mayer's reflex were abolished. Lesions of the postcentral gyrus led to paralysis or paresis of a transitory nature and to permanent hypotonia and diminution of the deep and superficial reflexes. These observations, which are in agreement with those of Foerster, indicate that the motor and the premotor syndrome originally described by Fulton cannot be sharply delimited from one another in man. The divergence in the results of experimental physiology and of clinical experience becomes less marked when recent ideas concerning areas 4 and 6 of Brodmann are taken into consideration. It has been claimed that the premotor fiber system, while arising chiefly from area 6, receives nerve fibers from area 4 also. Thus, it is possible that the spasticity associated with lesions of area 4 is based on involvement of premotor fibers arising therefrom. The hypotonia and hyporeflexia associated with lesions of the postcentral gyrus are not due to injury to nearby parts of the motor cortex, but represent a genuine syndrome of the sensory cortex itself.

ROTHSCHILD, Foxborough, Mass.

ELECTROCARDIOGRAPHIC STUDIES DURING THE COURSE OF METRAZOL TREATMENT OF SCHIZOPHRENIA. GERHARD FORSCHBACH, Ztschr. f. d. ges. Neurol. u. Psychiat. **164**:722 (Feb.) 1939.

Twenty-six electrocardiographic records were made on 8 patients immediately before and after a convulsive attack induced by metrazol. No records could be taken during the attack. In a few cases the effect of injection of the same amount of physiologic solution of sodium chloride was studied. No electrocardiographic changes appeared in these controls. Records were taken for from seven to fifteen minutes after the attack. The only change found before the attack was an increase in the pulse rate. After the attack two types of reaction were noted: In type 1 the pulse rate decreased in the first forty seconds after the attack with rapid return to normal, while in type 2 the pulse rate continued to be high with a gradual return to normal. It is possible that type 2 is really a later stage of type 1, the first part of which was missed on the record. The PQ interval is usually shorter during the first sixty to ninety seconds after the attack. This alteration was found in types 1 and 2. Later, the conduction time was increased. In 1 case heart block, with ventricular extrasystoles, was noted. The P wave showed definite changes in all the records. At times it was inverted, at other times notched. Its appearance differed in almost every part of the electrocardiogram. The ST interval was shortened after the attack, and the T wave was definitely increased in amplitude. In a few cases inverted T waves were seen in the second and third leads. The inverted T wave in the second lead is significant. The significance of the same change in the third lead is not yet clear. Auricular fibrillation was not noted. One case is mentioned in which there was cardiac standstill for four minutes after the injection of 5 cc. of metrazol. The heart began to beat after massage. Intracardiac administration of epinephrine is not advised in cases of marked bradycardia or cardiac standstill following injection of metrazol.

SAVITSKY, New York.

PAIN. M. M. GOUBERGRITZ, Acta med. U. R. S. S. **1**:136, 1938.

Goubergritz found changes in the blood chemistry in 81 patients who suffered from severe pains due to disease of the visceral organs. He found an increase in acetone and betaoxybutyric acid. The ketone bodies were definitely increased in cases of severe pain and returned to normal on cessation of the pain. The ketone bodies were normal in control cases. In 100 cases of childbirth the blood, taken before and after birth pains, showed evidence of marked rise in ketone bodies during the maximal painful contractions. Twenty-four hours after birth the acetone titer was normal. Goubergritz cites the association of neuralgic pains with diabetes, which are observed in cases of acidosis and are stopped by insulin. The pain starts in the optic thalamus and spreads to the hypothalamus, thus causing definite changes in the general metabolism. On the one hand, there is increase in ketone

bodies which are formed in the liver. On the other hand, there is migration of copper salts from the liver to the blood, with subsequent impoverishment of the liver. KASANIN, San Francisco.

Neuropathology

HYPOPHYSEAL TUMORS INDUCED BY ESTROGENIC HORMONE. B. ZONDEK, Am. J. Cancer **33**:555, 1938.

Estrogen injected either parenterally or percutaneously into 240 infantile rats caused eunuchoid dwarfing of all. Such treatment carried on for four months caused enlargement of the pituitary gland in the males; in the females the gland remained grossly normal. After treatment had continued for eight months the pituitary bodies of 29 of 35 rats, both males and females, were transformed into enormous hypophysial tumors. These tumors caused death of the animals. The duration of treatment was of primary importance, no tumor developing in less than seven months; the size of the dose of estrogen was of only secondary significance. The tumors could be diagnosed by typical clinical symptoms, the most characteristic of which was a decrease in the body temperature. This was shown not to be due to hypoglycemia. The enlarged pituitary glands and the tumors contained the same amount of gonadotropic substance as the normal pituitary glands of control animals. It was therefore not the production but the utilization of the gonadotropic hormone that was inhibited in the eunuchoid dwarf rats, causing a functional deficiency. FROM AUTHOR'S SUMMARY. [ARCH. PATH.]

EXPERIMENTAL MUSCULAR DYSTROPHY IN THE GUINEA PIG. HERMAN CHOR and RALPH E. DOLKART, Arch. Path. **27**:497 (March) 1939.

Structural changes in skeletal muscles occur from inanition or long-continued fasting. Hyaline necrosis of muscle fibers has been observed in experimental scurvy, and changes in the muscles have been found in animals with vitamin-deficient diets. Goettsch and Pappenheimer reported on muscular lesions described as progressive dystrophy of the voluntary muscles in guinea pigs and rabbits fed a diet deficient in vitamin E. Addition of vitamin E to the special diet, however, did not prevent development of the lesions. Starvation, infection and scurvy were ruled out. Some unknown factor in the special diet was considered responsible for the muscular lesions. Morgulis and Spencer were able to prevent as well as cure the "dystrophy" by feeding the following supplements along with the dystrophy-producing diet: fresh green alfalfa, lettuce and vitamin E (wheat germ oil), or dry alfalfa and vitamin E (wheat germ oil), or whole wheat germ.

Chor and Dolkart produced muscular changes in guinea pigs by the synthetic diet of Pappenheimer and Goettsch. The pathologic changes resembled coagulation necrosis, without changes in the intramuscular nerves or terminals. The histologic changes occurring in skeletal muscle in laboratory animals as a result of dietary factors differ greatly from those occurring as the result of lesions of the motor nervous system. Both show multiplication of nuclei in the early stages. Later, however, the changes are different. The atrophic and degenerative changes in muscle fibers cut off from their motor nerves consist in shrinkage of the fibers and a granular breakdown of the sarcostylic elements, with replacement by fibrous tissue and fat. The intramuscular blood vessels react by fibrosis of the vascular walls and endothelial hypertrophy. The intramuscular nerves and their endings completely disappear early in the process. The pathologic changes which result from deficiency in diet and from excess of cod liver oil are described as coagulation necrosis; many fibers are voluminous and waxy; some are narrow and shrunken. Fibrosis is not so prominent, and fat cells are rarely observed. No specific changes in the blood vessels can be detected.

The authors suggest the term "nutritional myodegeneration" rather than dystrophy for the muscular lesions produced by alterations in diet.

WINKELMAN, Philadelphia.

ARTERIOSCLEROSIS OF THE BRAIN AND SPINAL CORD, ESPECIALLY IN RELATION TO ARTERIOSCLEROSIS IN OTHER PARENCHYMAL VESSELS AND TO CEREBRAL HEMORRHAGE AND SOFTENING. G. LANZA, Arch. ital. di anat. **9**:259 (Jan.) 1939.

Lanza made an anatomic and microscopic study of the brain and spinal cord and other structures in 75 patients who died between the ages of 54 and 96 years of arteriosclerosis, vascular diseases and diseases other than vascular. He found that arteriosclerosis of the cerebral vessels is frequent in persons over 60. The disease is more acute in the intraparenchymal than in the extraparenchymal vessels, and in the nuclei of the base of the brain, especially the lenticular nucleus, than in the cerebral cortex and the spinal cord. In the cerebral cortex the lesions of the gray matter predominate over those of the white matter. Cerebral arteriosclerosis frequently exists in association with arteriosclerosis of the renal, splenic, cardiac and gastrointestinal territories. The microscopic aspect of cerebral arteriosclerosis is different from that of arteriosclerosis in the parenchymal vessels of other organs. The hyperplastic delamination of the internal elastic coat of the arteries is moderate. Hyalinosis of a special type, calcification (at the globus pallidus) and arterionecrosis (at the putamen) are frequent. Arteriosclerosis of the spinal cord is more rare and less acute than that of the brain. The former frequently develops in association with the latter. Acute lesions of the wall of the vessels (arterionecrosis) exist at the nuclei of the base of the cerebral territory opposite that in which cerebral hemorrhage took place. The lesions of the nonhemorrhagic area are different from those of the hemorrhagic foci. They tend to break and to form miliary aneurysms of the Charcot-Bonchard type. The lesions of the vessels in cerebral softening have a chronic evolution, which frequently shows the most common aspect of cerebral arteriosclerosis. They tend to diminish the lumen of the vessels and to form a mechanical obstacle to circulation. The author believes that there are two forms of cerebral arteriosclerosis: The benign form has a chronic evolution, induces the most common aspects of cerebral arteriosclerosis in the cerebral arteries and ends in cerebral softening. The malignant form has an acute evolution, induces necrosis of the arteries and ends in cerebral hemorrhage. J. A. M. A.

EPENDYMAL CYSTS CAUSING SUDDEN DEATH. K. BÖHMER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **30**:59, 1938.

Two deaths, supposedly resulting from accidents, were explained at autopsy by occlusion of the aqueduct of Sylvius by a tumor. In each instance the tumor was a cyst of ependymal origin, covered with connective tissue and lined by a layer of epithelium. The content of the cyst was rich in cholesterol and lipochrome. The first patient was a woman aged 46 who had complained of headaches for two months. She fell off a merry-go-round, struck her head on an iron rail and became unconscious for twelve hours. In the interval of two weeks between the time of the accident and her death she had headaches almost constantly. She died suddenly. The tumor was located in the third ventricle and was the size of a hazelnut. The accident two weeks before death was regarded as a result of temporary occlusion of the equeduct by the tumor.

The second death occurred in a cyclist a day after he had been found unconscious beside a cycle path. After regaining consciousness, he thought he had been struck on the shoulder by another rider and that he had lost his balance and fallen. However, he had sustained no serious injury, and his bicycle was undamaged and had been set against the curb by him. The tumor in the aqueduct was only 2 mm. in diameter. The lining of the third ventricle was roughened. A reconstruction of the course of events seemed to justify the assumption that the man had exerted himself while riding uphill, disturbed the cerebrospinal fluid balance in the brain and caused the tumor, which it is assumed had theretofore floated freely, to clog the aqueduct. With the first evidences of cerebral com-

pression from the lateral ventricles, the man dismounted, leaned his bicycle against the curbing and then sank to the ground in a stupor.

Böhmer cites cases reported by Beutler, Sjövall and Weissenburg to substantiate his interpretation of the cases reported. The theories of the cause of death in cases of occlusion of the third ventricle are discussed briefly.

RUKSTINAT, Chicago. [ARCH. PATH.]

SYRINGOMYELIA AND MULTIPLE SCLEROSIS IN THE SAME PATIENT. TRAUTE WERNER, Ztschr. f. d. ges. Neurol. u. Psychiat. **165**:416 (Feb.) 1939.

Werner reports the case of a man aged 32 who three years previously had suffered from pain in the back, difficulty with gait, defective speech and occasional incontinence. Four weeks before the last admission his lower limbs again became weak; his vision was blurred, and he suffered from paroxysmal laughing and crying. Thirteen years before admission he had noted gradual weakness of the hands and inability to perceive temperature and pain sensations.

The positive neurologic findings were: bilateral atrophy of the small muscles of the hands; a dissociated sensory syndrome in both hands and forearms, in the right lower limb and in the segmental distribution of from the fourth to the sixth dorsal nerve; mild bilateral oculomotor palsy; nystagmus; mild temporal pallor on the right; right palatoparesis, and weakness of the left hypoglossal nerve. The gait was spastic and ataxic; the abdominal reflexes were not obtained; a bilateral Babinski sign and a right ankle clonus were present. Autopsy showed an old syringomyelic cavity in the upper part of the cord and fresher foci of multiple sclerosis throughout the brain and cord. In the pons and in the periventricular region a few older patches were encountered. The author does not believe that there is any relation between syringomyelia and multiple sclerosis and considers their occurrence together in this case as coincidental.

SAVITSKY, New York.

Psychiatry and Psychopathology

FOLIE À DEUX. HELENE DEUTSCH, Psychoanalyt. Quart. **7**:307 (July) 1938.

Deutsch reports 4 cases of folie à deux. In the first instance three members of a family shared a common pseudologia fantastica; i.e., there were joint conscious and unconscious wish fulfilments. The basis of the shared illness was the libidinal relationship of three persons to one another and their joint reaction to the loss of a person with whom all three had an affect relation. In the second case a schizophrenic person adopted the delusion of another with the same disease. In this process there was no relation to the second subject, but the contents of his expressed delusions were closely akin to the first patient's fantasies. In the third case the delusions of a mother were so closely akin to the neurotic fantasies of the daughter that the latter adopted the mother's delusions. The fourth case was one of true paranoid folie à deux in two sisters who possessed in common repressed psychic contents, which broke out earlier in one than in the other. These cases seem to show that in a case of folie à deux the second member already has an inner psychic content which develops into a delusion because of its confirmation and encouragement by the delusions of the first member. In psychotic persons the common delusion appears to be an important part of an attempt to rescue the object through identification with it or its delusional system.

PEARSON, Philadelphia.

AKINESIA AFTER VENTRICULOGRAPHY. MARTIN GROTJAHN and THOMAS M. FRENCH, Psychoanalyt. Quart. **7**:319 (July) 1938.

Seven patients after ventriculographic examination presented peculiar and complete akinesia. All had tumors localized around the third ventricle. After

the ventriculographic procedure there were no spontaneous movements; even the eyes were not moved, and the winking reflexes were not obtainable. The patients could not eat spontaneously and were incontinent of urine and feces. Their consciousness was not disturbed. They were able to answer questions and to give information about their feelings, experiences and dreams. The pathologic cause of the akinesia seemed to be localized in the hypothalamic region. Patients with this disturbance have in common with waking persons clear consciousness and intact reality-testing ability. They have in common with sleeping persons complete lack of initiative and will power; a passive attitude and indifference; lack of response to stimuli from the outer world; withdrawal of libidinal interest from reality, and the external position of quiet, emotionless and happy rest. The bodily ego feeling is absent, and the akinetic person has no knowledge of this lack. Thus, the akinesia is to be compared with partial bodily sleep. These observations make clear the possibility of dissociating the cognitive and the volitional aspects of the ego's synthetic activity. PEARSON, Philadelphia.

THE INCIDENCE AND CHARACTER OF MASTURBATION THREATS IN A GROUP OF PROBLEM CHILDREN. MABEL HUSCHKA, Psychoanalyt. Quart. **7**:338 (July) 1938.

The histories of a group of 320 problem children were studied to determine how many of them had been threatened or punished for masturbation. It was found that 128, or 40 per cent, had been threatened drastically. Physical threats were used most commonly; over half the children had been threatened with genital injury. The threat usually emanated from the mother or mother substitute. This study is of special interest because it presents a body of factual material which indicates that at present children who masturbate are often threatened with castration. This fact has important implications with respect to castration anxiety. PEARSON, Philadelphia.

THE CONTRIBUTIONS OF PSYCHOANALYSIS TO THE EDUCATION OF THE ADOLESCENT. CAROLINE B. ZACHARY, Psychoanalyt. Quart. **8**:98, 1939.

Zachary's thesis is that the fundamental purpose of education is to help the growing person to learn to face society as it is, to adjust himself to it, in order to be able to participate in satisfying ways and perhaps to change it. The adolescent is greatly in need of such an educational program because he is passing through the most profound transition period of his life, because society gives less attention to education to fit the needs of the adolescent than it does to the education of the elementary and nursery school child and because, although one of the major problems of the adolescent is to establish his adulthood, society tends to permit him to achieve this only if his doing so meets its needs at a given time.

There is no person who passes through adolescence without conflicts, and it is the duty of the school to help him in dealing with them rather than to add to them. This is particularly the task of the school in modern society, because adults in civilization do not give the special assistance to young people approaching adulthood that they do in primitive societies. Psychoanalysis makes special contributions to the education of the adolescent. 1. It can help educators to understand better the dynamics of classroom behavior. Its concepts of personality development can aid educators to observe the adolescent in all his activities and surroundings, including the unconscious drives behind his creative productions, so that they can more accurately appreciate the conflicts, needs and aspirations of the adolescent and so understand better the personality and its struggles which lie behind the symptomatic behavior. 2. The analyst, because of his experience in dealing intensively with maladjustments, is in the best position to interpret to teachers the behavior of adolescents who need special help and to give adequate short time guidance to the youths themselves. PEARSON, Philadelphia.

SOME ETIOLOGIC FACTORS IN THE PATHOLOGY OF STAMMERING. I. LATIF, Brit. J. M. Psychol. **17**:307 (Dec.) 1938.

Latif finds that claims to one universal treatment in all cases of stammering are not justified by actual results and that, whereas some disorders of speech yield to one kind of treatment, a large number of patients remain unaffected by it. The author attempts an analysis of a few etiologic factors in the onset and cure of stammering by presenting 2 sample cases from his clinical investigations. These cases illustrate that the causes of stammering and its treatment vary from one case to another. The first case shows that although stammering may have its inception in the factors (fear of parents, sense of guilt because of masturbation, inferiority, imitation and fear of a stammering heredity) which may be regarded as more or less primary, other conditions, such as lack of steady control over breathing and voice and faulty habits of reading, may further complicate the etiologic factors in the disorder during the course of its development. Consequently, no therapeutic measure can be really effective unless, with the primary factors, it takes into account secondary conditions. Besides the analysis of the second patient's difficulties (which were similar to those of the first) when he was in a state of relaxation, the author also tried a few exercises of musical drill with him. In addition to this, he assigned a few tasks requiring delicate handling of instruments in the laboratory in order to help the patient overcome his sense of inadequacy in manual skill. The period of treatment lasted over eleven months, after which the patient was completely cured. Oral or phonetic exercises were not resorted to during the entire course of treatment.

J. A. M. A.

DYNAMICS OF SCHIZOPHRENIA UNDER THE INFLUENCE OF PROLONGED NARCOSIS. B. GUILIAROVSKI, Encéphale **1**:165, 1938.

The curative effect of prolonged narcosis is due to return to an earlier, prepsychotic state of mind and emotions. The intervening psychotic experiences of the patient are not forgotten, but have lost their emotional tone, "acuity" and "vitality." Thus, after a brief period of toxic delirium which follows the awakening, the patient may approximate his prepsychotic personality.

LIBER, New York.

MESCALINE HALLUCINATIONS AND THE PSYCHOSENSORY DISTURBANCES OF CHRONIC EPIDEMIC ENCEPHALITIS. HENRI EY and MARCEL RANCOULE, Encéphale **2**:1, 1938.

Ey and Rancoule compared the hallucinations produced in nonencephalitic subjects by injections of mescaline sulfate with the spontaneous hallucinations of encephalitic subjects and with those of encephalitic patients who received mescaline. Predominance of visual features, motion, the passage of successive images as on a screen, grotesque or caricatural deformations, changes in size and color of images, feelings of strangeness and depersonalization, anxiety and somnolence are common characteristics of the spontaneous hallucinations of encephalitic patients and of those produced by mescaline. In encephalitic patients with hallucinations mescaline intensifies the hallucinatory experiences without altering their nature. These hallucinations are all illusory. This can be demonstrated by the fact that the images are seen as if projected on any object conveniently placed to act as a screen. The prolongation of after-images to an extent which approaches eidetism occurs in encephalitic patients. Thus, a patient who lived in a room with red walls saw all objects red. Sialorrhea, sudden akinesia, hypertonia, obsessive impulses and dilatation of veins in the eyegrounds occur in both encephalitic parkinsonism and mescaline intoxication.

LIBER, New York.

MENTAL CHANGES IN PERNICIOUS ANEMIA. J. VAN BAALEN and M. M. P. VROON, Nederl. tijdschr. v. geneesk. **83**:270 (Jan. 21) 1939.

Van Baalen and Vroon show that psychic disturbances may occur when changes take place in the quantity of blood as well as in diseases of the blood. Excessive loss of blood, for instance, may be followed by periods of somnolence, confusion, anxiety and headache. In polycythaemia rubra, nervous symptoms in the form of headaches, dizziness, tinnitus aurium and paresthesias have been noted, but disturbances of a psychotic character have also been observed. Reviewing the literature on mental changes in pernicious anemia, the authors cite several investigators who have made reports on this problem and point out that Roger and Olmer differentiated three stages in the psychic disturbances of pernicious anemia. During the initial stage mild character changes appear, such as quarrelsomeness, jealousy and peevishness. Sometimes the mental energy decreases. During the second stage there may appear psychic changes, varying from simple psychic asthemia to a demented condition, and even delirious phases with delusions of persecution. The terminal stage is characterized by demented conditions, confusions and hallucinations. Under the influence of modern liver therapy, these disturbances are less frequent. After calling attention to some reports concerned with psychoses in so-called funicular myelitis, the authors report their observations on 3 patients with pernicious anemia who had mental disturbances. The first patient presented paranoid reactions, depressive disturbances, delirious phases and suicidal inclinations. In the 2 other patients the changes in the character and in the moods predominated. As the blood picture improved under the influence of liver therapy the psychic disturbances likewise subsided. J. A. M. A.

Meninges and Blood Vessels

THE ETIOLOGY OF TRAUMATIC MENINGITIS: A SURVEY OF NINETY CASES VERIFIED AT AUTOPSY. CYRIL B. COURVILLE and C. DON PLATNER, Bull. Los Angeles Neurol. Soc. **3**:150 (Dec.) 1938.

The cause and pathogenesis of pyogenic meningitis following trauma constitute a complex problem which extends far beyond the direct extension of organisms into the cranial cavity through a fracture. Courville and Platner made a study of 1,261 cases of fatal craniocerebral injury, in 90 of which meningitis was discovered at autopsy, an incidence of about 6 per cent. This figure is in accordance with the observations of others as to the incidence of meningitis following ultimately fatal injury to the head in civil life, although the percentage varies between 18 and 35 in war. Courville and Platner constructed the following classification of their cases on an etiologic basis. 1. Meningitis after basal fracture involving the nasal cavities, sinuses or auditory canal. In this, the largest group, there were 61 cases, in 31 of which the fracture was in the anterior fossa, in 17 in the middle fossa and in 13 in both the anterior and the middle fossa. Only 4 of the 61 patients were female. 2. Meningitis after compound depressed fractures of the vault, 5 cases. 3. Meningitis after penetrating wounds of the skull, 3 cases. 4. Meningitis after injuries to the head without fracture, 9 cases. In this interesting group the path of invasion was usually not evident, but seemed to be from an infected scalp wound, the nasal sinuses or the ear through emissary veins into the skull. 5. Meningitis secondary to traumatically precipitated sinusitis, otitis or mastoiditis, 4 cases. 6. Meningitis following injury to the spine, 2 cases. 7. "Metastatic" meningitis secondary to traumatically induced suppurative foci elsewhere in the body, particularly in the thorax, 5 cases. 8. Meningococcic meningitis precipitated by injury, 1 case. The possibility of tuberculous meningitis precipitated by injury is mentioned; no such case, however, was found in this series, and the authors consider its entity to be uncertain. Courville and Platner state that meningitis induced by trauma may be immediate, primary or direct, or delayed, secondary or indirect. Indirect or secondary meningitis follows some other suppurative intracranial lesion. Delayed meningitis is due to extension of infection through a fracture at least three weeks after the injury.

The treatment of this type of meningitis consists largely of prevention, in discussing which Courville and Platner mention adequate antisepsis of scalp wounds, gentle handling of patients, avoidance of irrigation and examination of bleeding ears, great care in exploring compound depressed fractures and the avoidance by the patient of blowing the nose, coughing, sneezing or straining. The patient should be kept on his back with the head slightly elevated. Administration of sulfanilamide is mentioned.

MACKAY, CHICAGO.

MENINGITIS CAUSED BY ATYPICAL GRAM-NEGATIVE COCCI. H. A. REIMANN and R. W. KOUCKY, J. Bact. **37**:401 (April) 1939.

Reimann and Koucky studied the atypical bacteria found in 2 cases of meningitis. From the first patient, a gram-negative diplococcus with characteristics different from other classified strains was isolated. The bacterium gave rise to two interchangeable colony forms. From the second case, two species of cocci were obtained; one was a type I meningococcus which had the unusual ability to grow on plain agar at room temperature and had gram-positive elements; the other was a staphylococcus which was represented by three interchangeable colony forms. These studies suggest that with routine laboratory procedures atypical colonies may appear on culture plates. Such colonies, usually ignored or dismissed as contaminants, may actually be part of the pattern of variation of the bacterium concerned. Recognition of the phenomenon of bacterial variation and type transformation would remove much confusion and would probably reduce the varieties of bacteria now believed to exist.

J. A. M. A.

LYMPHOCYTIC CHORIOMENINGITIS: REPORT OF TWO CASES WITH RECOVERY OF VIRUS FROM GRAY MICE (MUS MUSCULUS) TRAPPED IN THE TWO INFECTED HOUSEHOLDS. C. ARMSTRONG and L. K. SWEET, Pub. Health Rep. **54**:673 (April 28) 1939.

Armstrong and Sweet report 2 established cases of lymphocytic choriomeningitis. The finding of active choriomeningitis virus in 3 of 5 mice trapped in the homes of the patients and the failure to find the infection in 21 mice trapped in eight homes and buildings wherein no human cases of the disease had occurred indicated that the association between the human cases and the infected mice was more than a coincidence. It is believed that the mice constituted the source of human infection for the following reasons: 1. In each instance the patient was ill in the home for only four days before being hospitalized. 2. The housewife in both households apparently suffered infection, while one mate escaped and the only evidence of infection in the other members of the household was a moderate degree of immunity, as judged by the serum-virus neutralization test. These observations suggest that infection was due to exposure in the home rather than to human contact. 3. The capture of a less than half-grown infected mouse in the home of 1 of the patients eighty-seven days after the patient had been removed from the house indicated the existence of an active infection in the mice independent of the presence of a recognized human case. 4. The presence in one home of a person who possessed strongly developed antibodies at a time when the patient's immunity was but partially developed suggests that the case of the disease did not constitute the initial introduction of the virus into the household. The observations suggest that the gray mouse, Mus musculus, constitutes a reservoir of choriomeningitic infection from which the disease may be contracted by man.

J. A. M. A.

THE BLOOD SUPPLY OF THE HUMAN SPINAL CORD. B. BOLTON, J. Neurol. & Psychiat. **2**:137 (April) 1939.

Bolton studied the source of vascular supply and the direction of blood flow of the human spinal cord by means of injection of colored pyroxylin dissolved in acetone and india ink. He found that the anterior aspect of the spinal cord is

supplied by the anterior spinal arteries and that the direction of blood flow is from above downward. The anterior spinal arteries derive their supply throughout the entire cervical and upper two thoracic segments from the vertebral arteries, and below that level from the intercostal and lumbar arteries. On the posterior surface of the cord the supply is from the posterior spinal arteries. These derive their blood from the vertebral or posterior inferior cerebellar arteries throughout the cervical and upper thoracic segments, where the direction of flow is from above downward. Below this, the posterior spinal arteries derive their blood from the terminal portion of the anterior spinal arteries, via the lowest lateral branches, and the flow is directed upward as far as the upper thoracic level. Within the spinal cord the posterior spinal artery supplies the posterior portion of the posterior column and the posterior horn, while the anterior spinal artery supplies the rest of the substance of the cord; there is little anastomosis between the capillaries of the two main vessels. Where the flow of blood from the two sources meet there are zones which are particularly susceptible to ischemia from occlusion of one of these sources. This explains the frequent occurrence of distant symptoms in cases of pressure lesions of the cord.

MALAMUD, Ann Arbor, Mich.

CRANIAL HYPERTENSION IN RELATION TO ARTERIAL HYPERTENSION. RISER, J. PLANQUES and P. BARBIER, Presse méd. **47**:649 (April 29) 1939.

Riser and his associates present a study of the interrelations of cranial and arterial hypertension. Their observations are based on 140 patients, who were given 5,000 manometric measurements in strictly horizontal lateral decubitus. They find 20 cm. of water the maximal craniospinal pressure (with the average ranging between 15 and 18 cm.) for patients in the recumbent and 48 cm. for patients in the sitting position. The authors distinguish between uncomplicated and complicated arterial hypertension in relation to cranial hypertension. The former does not induce cranial hypertension, as the case histories of 75 of their patients reveal. On the other hand, complicated arterial hypertension often induces cranial hypertension in various phases. Of 50 patients, 34 per cent clearly showed cranial hypertension; 20 patients showed moderate cranial hypertension (with pressures of from 23 to 30 cm.); 10 had pressures of from 30 to 35 cm., and 4 had, respectively, 40, 48, 50 and 52 cm. Tests were made with the patient in the horizonal position. In 3 instances decubitus tests invalidated the normal readings indicated by tests made in the sitting position. The authors stress the importance of systematic examinations of the fundus oculi. Papillary edema was particularly frequent in cases of complicated arterial hypertension. In 23 of 25 patients marked venous tension, fluctuating between 15 and 40 cm., accompanied cranial hypertension. Toxic factors, such as faulty metabolism of proteins, chlorides and water, were also clearly causative of cranial hypertension. However, 7 patients with pure azotemic nephritis and a urea content of from 2 to 3 Gm. remained unaffected by cranial hypertension. Seven patients with high cranial hypertension, on being subjected to rigorous disintoxication, with blood lavage in 2 cases, showed increased diuresis; abnormal chloremia and azotemia and cranial hypertension disappeared. Likewise, a local intracranial lesion, such as cerebromeningeal edema, increased cranial hypertension in cases of complicated arterial hypertension. Arterial hypertension may also be of central neurologic origin, secondary to a lesion or a functional disorder and so, of necessity, accompanied by cranial hypertension. Some of the practical consequences and symptomatic values deduced by the authors from their observations are noted. Uncomplicated arterial hypertension is never accompanied by cranial hypertension, even if it has been high for a long time. They suggest that the tests be applied to determine the primary or secondary nature of cranial hypertension when this is clinically, ophthalmologically and manometrically established beyond doubt. Tests to distinguish between the presence of a cerebral tumor and "pseudotumoral arterial hypertension" neither are difficult nor require a long time. In 40 of 50 cases of arterial hypertension with pronounced cranial hypertension diagnostic tests were directly determinative. Arterial and cranial hypertension

unaccompanied by certain indications, such as cardiovascular-renal disturbances, ophthalmologic signs and toxicity, require especially careful tests—indicated by the authors—to determine the neurologic origin of the condition, to be supplemented, if necessary, by ventriculographic examination. Sometimes the latter procedure will show the absence of a tumor, and the subsequent evolution point to serious and complicated arterial hypertension. Such cases are not numerous, but need to be noted, as they reveal that all the factors of cranial hypertension coexistent with arterial hypertension are not known. In 2 instances the ophthalmologic and manometric indications of cranial hypertension preceded all the others by several years. The authors summarize their important observations in three groups: (1) coexistence of craniointracranial lesion and arterial hypertension without a close causal interrelationship; (2) central neurologic lesions inducing and controlling arterial hypertension, and (3) arterial hypertension controlling cranial hypertension (the largest group).

J. A. M. A.

HEMORRHAGIC MENINGITIS. G. MARTINOFF, Ztschr. f. d. ges. Neurol. u. Psychiat. **164**:687, 1939.

Meningitis was found to be the cause of the bleeding in 6 of 52 patients with subarachnoid hemorrhage. In 2 cases the disease was tuberculous meningitis; in 2 it was due to meningococci, in 1 to Staphylococcus aureus haemolyticus and in 1 to the anthrax bacillus. Xanthochromic fluid was found in 8 of 92 cases of tuberculous meningitis and in 6 of 63 cases of epidemic meningitis. Twenty-seven similar cases of hemorrhagic meningitis were collected from the literature. In addition to the organisms mentioned by the author, Bacillus coli, pneumococci and the gas bacillus were found in the spinal fluid. In all the author's cases the bleeding occurred as a complication after the onset of the illness. In the case of gas bacillus infection the onset was sudden, with bleeding into the meningeal spaces. In the case of staphylococcic meningitis with meningeal hemorrhage extensive infection of the walls of vessels, with rupture, was demonstrated. In the cases of bacterial meningitis the number of white cells in the bloody spinal fluid was much greater than in the cases of spontaneous subarachnoid bleeding. In cases of meningitis the onset is usually with a high temperature, whereas the temperature generally rises later in the course in cases of subarachnoid hemorrhage. While in most cases of meningitis the bleeding is due to direct injury and rupture of blood vessels, diapedesis may account for the bleeding in some instances.

SAVITSKY, New York.

FOLLOW-UP STUDIES IN CASES OF MENINGITIS SEROSA EPIDEMICA (WALLGREN). LISELOTTE OHEIM, Ztschr. f. d. ges. Neurol. u. Psychiat. **165**:350, 1939.

Eleven patients with a condition diagnosed as meningitis serosa epidemica were studied eight years after the acute attack. In 2 cases recovery was complete after the acute attack. In the others various complaints, such as headaches, ready pallor, dizziness and feelings of faintness, persisted for variable periods. In some cases emotional instability, a ready tendency to become depressed and restlessness were noted. Some of the children did not do well in school work. In 3 of the cases the complaints lasted for one and one-half years. In 3 others the complaints persisted until the time of investigation, but with a progressive tendency to improvement. In none of the cases last mentioned were the complaints serious enough to interfere with the mental progress of the children. In 1 case hydrocephalus appeared during the acute stage, but receded later. There was no clearcut relation between the severity of the acute attack and the intensity or duration of the sequelae. In 1 case there were two recurrences. In this case the first attack was characterized by signs of meningeal irritation and paralysis of the sixth nerve. Three years later diplopia reappeared for a few days, and four years and eleven months after the first episode nystagmus, mild dizziness, differences in the reflexes and meningeal signs were noted. The last recurrence

disappeared without any residual signs. No instances of chronic encephalitis with parkinsonism were noted. This study of the further course in cases of so-called meningitis serosa epidemica favors its consideration as a disease entity *sui generis* and not as an abortive form of von Economo's disease (lethargic encephalitis) or poliomyelitis.

SAVITSKY, New York.

THE INNERVATION OF THE INTRACRANIAL BLOOD VESSELS. E. BUSCH, Acta psychiat. et neurol. **13**:131, 1939.

In a previous work Busch showed that all intracranial blood vessels are abundantly supplied with nerves, each smooth muscle cell of the vascular wall being innervated. Two types of nerves are found: the nonmedullated vasomotor nerves, which terminate on the muscle cell in a closed net of fine fibrils and degenerate after section of the corresponding sympathetic ganglia, and the medullated, freely terminating sensory nerves, which are found only in the adventitia of larger vessels and which persist after ablation of the corresponding sympathetic ganglia. Because the impregnation methods reveal only a few nerves on the intracranial blood vessels, Busch applied Ehrlich's methylene blue (methylthionine chloride) method to show that the nerve supply to these vessels is as abundant as to those elsewhere in the body and that the apparent poverty of nerves in the brain is attributable to the technic used. Intracranial blood vessels were examined from the mouse, cat, rabbit and human brain. The reticular, nonmedullated nerves were observed throughout the intracranial vascular tree, including vessels with a diameter of 10 to 15 microns. Innervation of the capillaries was demonstrated in only 7 of several hundred preparations. Freely terminating medullated nerves were observed only on the large arteries at the base of the brain and on the most proximal parts of their branches.

YAKOVLEV, Waltham, Mass.

Diseases of the Brain

GUMMA OF THE BRAIN. BERNARD J. ALPERS, Am. J. Syph., Gonor. & Ven. Dis. **23**:233 (March) 1939.

Alpers reports 3 cases of solitary gumma of the brain, 2 of which were in the temporal lobe and 1 in the frontal lobe. All the patients were treated surgically; 1 patient did not survive the operation. The serologic reactions of the blood were positive in 2 patients who had negative Wassermann reactions of the spinal fluid. The serologic reaction of the spinal fluid of the third patient was not recorded, but the blood gave negative reactions. A colloidal gold curve of the dementia paralytic type was present in 1 instance. The 3 patients had signs of a progressive lesion of the brain, and 2 had increased intracranial pressure.

Recent statistics have shown, contrary to past experience, that gummas of the brain are rare. They are generally single, and their incidence of multiplicity is not as great as that of tuberculomas. The lesions are usually due to acquired syphilis, but may occur rarely in congenital syphilis. Gross and histologic examination of gummas of the brain proves that they are similar to those in other portions of the body. The clinical features are essentially those of tumor of the brain. They usually occur in patients over 25, and the distribution between the sexes is equal. The focal symptoms vary with the location of the lesion, which may be anywhere in the brain. The period of development of the symptoms varies from a few months to twenty years. There is considerable variation in the serologic reactions of the blood and spinal fluid. The Wassermann reaction of the blood may or may not be positive. The serologic reaction of the spinal fluid is more often negative than positive, but a completely normal spinal fluid is unusual.

Alpers states that in the case of a patient with a history of syphilis, progressive symptoms of increased intracranial pressure, focal signs and positive serologic reactions of the blood and spinal fluid one may conclude only that the patient has

a tumor of the brain which may be a gumma. Certainty is impossible, for various reasons. Of 75 cases of meningeal fibroblastomas reported by Frazier and Alpers, there were positive serologic reactions of the blood and spinal fluid in 3. Tumors of the brain in rare cases may give a false positive serologic reaction. Syphilitic meningitis is not infrequently confused with gumma of the brain. Today the diagnosis of gumma of the brain is not as important as in the days before brain surgery. Gumma is an operative lesion, and a diagnosis of tumor of the brain, possibly a gumma, is sufficient. Iodides have little effect on these lesions, and they must therefore be treated as tumors. The only real cure consists of operative removal, followed by antisyphilitic therapy.

BECK, Buffalo.

COMPLETE AGENESIS OF THE CORPUS CALLOSUM. DAVID L. REEVES and CYRIL B. COURVILLE, Bull. Los Angeles Neurol. Soc. **3**:169 (Dec.) 1938.

Reeves and Courville report 4 cases of complete agenesis of the corpus callosum, in all of which the diagnosis was made at autopsy. The 4 patients were aged 19 years, 3 months, 4 months and 69 years, respectively. The first patient died of subdural hemorrhage two months after a fall on the occiput, the second of unstated causes, the third of hydrocephalus and the fourth of cerebral thrombosis and hemorrhage from a duodenal ulcer. No definite mental or neurologic abnormalities had been recorded which could be attributed to the developmental defect. Other associated anomalies were discovered, including the primitive radial arrangement of the sulci of the medial surface of the cerebral hemispheres, nonunion of the calcarine and parieto-occipital sulci, excessive development of the anterior commissure (although this structure was almost totally absent in case 2) and abnormally separated and dorsally blunted anterior horns and dilated posterior horns of the lateral ventricles. In the first case an extensive arachnoid cyst was observed between the hemispheres, occupying the normal location of the corpus callosum, and in the second a similar small cyst was seen above the posterior portion of the third ventricle. In the third case advanced internal hydrocephalus was present. Reeves and Courville point out that the corpus callosum develops during the third and fourth months of fetal life, and that factors leading to its agenesis must operate at or before that period. Actual etiologic agents are unknown. Clinical and experimental destruction of the corpus callosum in man and animals has served to minimize the functional importance of the corpus callosum, as has the absence of any characteristic symptoms in cases of agenesis.

MACKAY, Chicago.

METRAZOL THERAPY IN CHRONIC ENCEPHALITIS WITH PARKINSONISM: EFFECT ON OCULOGYRIC CRISES. EUGENE ZISKIND and ESTHER SOMERFELD-ZISKIND, Bull. Los Angeles Neurol. Soc. **3**:186 (Dec.) 1938.

Ziskind and Somerfeld-Ziskind induced five convulsions with metrazol in a woman suffering from chronic encephalitis with parkinsonism and frequent oculogyric crises. On two occasions the seizure occurred during an oculogyric crisis, and in both the ocular deviation was absent after the convulsion. On one occasion the deflection of the eyes was changed from an upward to a downward deviation during the seizure. After the course of metrazol the oculogyric crises were reduced in frequency; the patient gained in weight, and her mood changed from depression to euphoria. The muscular rigidity was not altered by the treatment.

MACKAY, Chicago.

AMNESIC APHASIA DUE TO TWO SMALL FOCAL LESIONS. KENNETH H. ABBOTT, Bull. Los Angeles Neurol. Soc. **3**:188 (Dec.) 1938.

In the case reported by Abbott, a woman aged 64, who suffered from auricular fibrillation due to rheumatic fever, was suddenly afflicted with slight right hemiparesis and inability to name objects. She could describe articles only in terms

of their use. There was some improvement in the hemiparesis during the next two days, when she suddenly became hemiplegic on the left side; she died three days later. Autopsy revealed rheumatic endocarditis, numerous infarcts throughout the body and embolism of the right middle cerebral artery, which had evidently caused death. The only lesions in the left hemisphere were two small areas of cortical necrosis, one in the superior temporal convolution and the other in the third temporal convolution, just anterior to the temporo-occipital sulcus. These minute cortical lesions must have caused the amnesic aphasia; they are the smallest ever reported as having produced this symptom.

MACKAY, Chicago.

DIFFICULTIES IN DIFFERENTIAL DIAGNOSIS OF BRAIN TUMOR IN OLDER AGE GROUPS. DONALD W. HASTINGS, J. Nerv. & Ment. Dis. **89**:44 (Jan.) 1939.

Hastings reviewed the autopsy records in 177 cases of tumor of the brain. In 25 instances, those of patients over 40, the diagnosis was made only at autopsy, and in these the "cardinal symptoms of brain tumor," headache, vomiting and choked disks, were largely absent. In this group the average age of the patients was 56; the duration of symptoms averaged ten months; the blood pressure was usually normal or low, and roentgenograms of the skull and studies of the cerebrospinal fluid were rarely of aid in diagnosis. In 2 patients the presence of syphilis, with a formula for the cerebrospinal fluid, characteristic of dementia paralytica, caused confusion, and in 3 others increased amounts of lead in the urine led to a mistaken diagnosis. In 19 of the 25 cases the diagnosis was cerebral vascular accident, which is therefore the most common diagnostic error in cases of tumor at advanced ages.

MACKAY, Chicago.

CLINICAL RECOGNITION OF PICK'S DISEASE. L. BENEDEK and T. LEHOCZKY, Brain **62**:104 (March) 1939.

Benedek and Lehoczky cite 3 cases of Pick's disease diagnosed during life, in all of which peculiar arteriographic and ventriculoencephalographic features were presented. In 2 cases confirmatory evidence was obtained by cerebral puncture. The encephalogram showed opercular cysts in 1 case in the fifth ventricle, in another on both sides. A progressive increase in the size of these cysts was demonstrated by encephalograms taken at intervals of from four to six weeks. Cerebral angiograms showed changes attributable to atrophy. Cerebral puncture demonstrated severe degeneration of the frontal cells and axons, activity of the glia and, in case 2, incipient senile plaques. In the ventriculogram in case 3 the projection of the frontal horns of the lateral ventricles bulged enormously, especially on the left side, thus giving the ventricular system a peculiar dumbbell-like or clublike appearance. On the basis of these 3 cases, the authors assert that the clinical syndrome in itself is sufficient for the differential diagnosis of the disease.

J. A. M. A.

DELUSIONAL PSYCHOSIS AND MULTIPLE SCLEROSIS. AUBIN and A. BARRAUX, Encéphale **1**:239, 1938.

Aubin and Barraux report the case of a man aged 28 in whom the development of symptoms of multiple sclerosis and of ideas of persecution and influence by his military superior, with visual hallucinations, were inextricably interwoven. The patient believed that the cramps in his legs, muscular jerks and difficulty in walking were caused by his persecutor. His prepsychotic tendency to isolation from his fellows became exaggerated and was accompanied by incoherence and periods of depression. Neurologic examination revealed spastic gait, hyperreflexia, clonus, abolition of the abdominal reflexes and ataxia. Transient amelioration was followed by a relapse. The psychosis was organic in type. Psychoses accompanying multiple sclerosis often give the impression of being functional.

LIBER, New York.

CEREBRAL METASTATIC TUMORS. R. SOTO ROMAY, Arch. argent. de neurol. **20**: 89 (March-April) 1939.

Soto Romay made a clinical and anatomic study of 20 cases of cerebral metastases from a group of 286 cases of cancer of different locations in which a necropsy was performed. He found that the greatest incidence of cerebral metastases is in patients of either sex between 30 and 40 years of age. Epitheliomas of the lung, the breast and the adrenal gland most frequently give cerebral metastases. The number, size, distribution and exact location of the metastases vary in different cases. The brain, the cerebellum and, in rare cases, the optostriated nuclei are the nerve structures most frequently involved by metastases, which may be isolated or multiple and involve one or various structures at the same time. Frequently the cerebral symptoms are the first to show the presence of cancer in some other organ. The symptoms of cerebral metsatases are similar to those of primary cancer of the brain. In the majority of the cases intracranial hypertension and edema of the papilla exist. A diagnosis of probable cancerous metastases is made in the presence of intracranial hypertension, with edema of the papilla and actual existence or a history of cancer in the past in the given patient. Cancer of the lung, either primary or secondary, does not exist in all cases of cerebral metastases. The evolution of cancerous metastases depends on the location of the tumor, probable compression of important structures, type of the malignant growth and general condition of the patient. As a rule the metastases follow an evolution to final cachexia in from two to six months. Certain local conditions, such as cerebral softening and cerebral hemorrhages near or far from the tumor, accelerate the evolution of the growth. The microscopic type of cancer metastases of the brain is not necessarily the same as that of the primary tumor. The metastatic nodules cause infiltration and destruction of the nerve tissues. J. A. M. A.

CEREBRAL DEFECTS IN CHILDREN DELIVERED BY CESAREAN SECTION. T. BRANDER, Acta pædiat. **23**:145 (Dec. 31) 1938.

Brander says that it is generally believed that the abdominal cesarean section insures against intracranial birth injuries. However, in reviewing the literature he found 72 cases of intracranial lesions verified post mortem in children who had been delivered by abdominal cesarean section (cases of vaginal cesarean section excluded). In some of these cases tearing of the tentorium was discovered. There are also numerous observations on symptoms of intracranial birth injuries, such as defective intelligence, epileptiform convulsions and spastic pareses. The author describes the clinical histories of 3 children with mental defects who had been delivered by cesarean operation. He admits that in cases of severe cerebral defects the hereditary conditions are not always sufficiently clear. Moreover, the reports in which the diagnosis of intracranial lesions in children delivered by cesarean operation cannot be doubted contain nothing about the obstetric complications that led to the cesarean operation. In this connection, the author points out that the fetus may have been injured by attempted forceps extraction before the cesarean operation was resorted to. The same applies to cases in which prolonged labor pains, perhaps in connection with Walcher's position, preceded the operation. If at this time the head of the child was tightly wedged into the pelvic inlet it may be injured not only before but also during the cesarean operation. Intracranial birth injuries in connection with the cesarean operation occur more frequently in vaginal than in abdominal cesarean section, and of the abdominal methods the corporal method involves less dangers for the fetus than does the cervical. Moreover, extraction by the foot seems to be more dangerous than freeing the head first, and instrumental development of the head is, of course, more harmful than its manual extraction. In cases in which the fetus is large, too short incisions may increase the danger of an intracranial lesion. Complications may arise if the surgical incision injures the placenta. The danger of intracranial hemorrhages in the course of cesarean operations is greater in premature deliveries, in hemor-

rhagic diathesis and in pregnancy toxicoses. Asphyxia supposedly may cause intracranial hemorrhages; on the other hand, it is probable that intracranial injury may become manifest in asphyxia. That methods of resuscitation may cause intracranial hemorrhages in children delivered by cesarean operation has likewise been observed. Moreover, in 2 reported cases of fatal intracranial hemorrhages after cesarean delivery uterine tumors were discovered. J. A. M. A.

NEUROLOGIC SYMPTOMS IN BENIGN LYMPHOGRANULOMATOSIS. BERTIL ROOS, Acta psychiat. et neurol. **13**:42, 1938.

The lesions of so-called benign lymphogranulomatosis of Schaumann occur chiefly in the skin, lymph nodes, liver, spleen, lungs, eyeballs and bones of the hands and feet. Involvement of the nervous system is rare. Roos reports 1 case of his own and reviews 7 cases reported in the literature in which lymphogranulomatosis was complicated by involvement of the peripheral nerves, the optic nerves and the central nervous system. Granulomatous infiltration of the peripheral nerves causes pain, paresthesias, sensory loss, paralysis and muscular atrophies. The infiltration within the retina and optic nerve causes uveitis, exophthalmos and loss of vision. Granulomas within the meninges and the brain lead to tumor-like symptoms, such as increased intracranial pressure, choked disks, increased protein in the cerebrospinal fluid, headache, vomiting, failing vision, convulsions, mental obtusion, focal signs of involvement of the cranial nerves and infundibular-pituitary disturbances. The prognosis is favorable. The disease may run a prolonged course, with only minor neurologic symptoms. YAKOVLEV, Waltham, Mass.

Treatment, Neurosurgery

PATHOGENESIS AND TREATMENT OF MYOTONIA CONGENITA. HENRY G. PONCHER and HELEN WOODWARD WADE, Am. J. Dis. Child. **55**:945 (May) 1938.

Poncher and Wade previously described the cases of 2 patients with myotonia congenita, 1 a child who responded, and 1 an adult who failed to respond, to thyroid therapy. They report further on these 2 cases as well as on those of 2 patients with the same syndrome. All 4 patients showed abnormal creatine-creatinine metabolism. In the 2 children there was absence of the physiologic creatinuria of childhood. These children showed a marked difference in response to thyroid therapy, which was clinically ineffective in the adults. The infant showed relief from symptoms after thyroid therapy, which was correlated with the production of creatinuria. The other child's response was midway between that of the infant and that of the adult. The authors suggest that the difference in creatinine metabolism between children and adults may be the reason for this variation in response. The duration of the disease and the resultant pathologic changes must also be considered. Quinine therapy resulted in almost complete relief for the 2 patients treated by this means, one an adult and the other a child. It failed to increase the elimination of ingested creatine, but it increased the preformed creatinine in 1 case. It is obvious that quinine has a different mode of action from that of thyroid, since it gave relief to adults as well as to children and affected the preformed creatinine rather than the creatine tolerance. It must be administered constantly, while thyroid shows a residual action in children. The authors have investigated the treatment in 15 cases and find that quinine alone in older patients and thyroid in the infant gave complete relief of myotonic symptoms.

WAGGONER, Ann Arbor, Mich.

THE TREATMENT OF TABETIC LIGHTNING PAINS WITH THIAMIN CHLORIDE. P. F. METILDI, Am. J. Syph., Gonor. & Ven. Dis. **23**:1 (Jan.) 1939.

Metildi points out that the pathogenesis of the lightning pains in tabes dorsalis is unknown. The close pathologic analogy between the lesions in the cord

in tabes dorsalis and those in subacute combined degeneration has long been recognized. Wintrobe and his co-workers, studying macrocytic anemia in swine by means of a diet deficient in vitamin B_1, have produced degeneration of the posterior columns of the spinal cord closely simulating that in tabes. Metildi considers it possible that the lightning pains and paresthesias of tabes may be due, at least in part, to peripheral neuritis and that a therapeutic trial of thiamin chloride is therefore justified in this condition.

Six tabetic patients were selected for treatment with thiamin chloride. In each patient antisyphilitic treatment by standard means had been ineffectual in relieving lightning pains. The thiamin chloride was given intravenously or intramuscularly, usually 10 mg. every seven to ten days. All 6 patients were markedly benefited by the vitamin B_1 therapy.

BECK, Buffalo.

SULFANILAMIDE IN THE TREATMENT OF EXPERIMENTAL STREPTOCOCCIC AND PNEUMOCOCCIC MENINGITIS. JOHN A. KOLMER, ANNA M. RULE and MARY L. WERNER, Arch. Otolaryng. **27**:519 (May) 1938.

Sulfanilamide has been more successful in treatment of streptococcic than of pneumococcic meningitis. Meningitis was produced in rabbits and monkeys by intracisternal inoculation with beta hemolytic streptococci. Symptoms of meningitis usually appeared in four hours. Other animals were given injections of type I, II or III pneumococci. Animals given sulfanilamide remained alive much longer than control animals. The best results were obtained in the animals with the streptococcic form, which were given the drugs orally, subcutaneously and intracisternally. Intracisternal or intraspinal injections alone had no apparent effect. Oral administration alone was not as effectual as subcutaneous injections. In the cases of pneumococcic meningitis, the evidence of the therapeutic effectiveness of sulfanilamide is suggestive, but is not as satisfactory as in those of streptococcic meningitis. It was found that sulfanilamide reduces the number of streptococci and promotes phagocytosis. It apparently restrains the growth of beta hemolytic streptococci. Drainage of the primary focus and continuous drainage of the cerebrospinal fluid should be performed every eight to twelve hours. Large doses are required for the first three to five days. Monkeys given injections of streptococci intraspinally died in about seventy-four hours. Of 12 animals treated with sulfanilamide, 7 recovered. Rabbits inoculated intracisternally with types I, II and III pneumococci presented acute meningitis, with associated septicemia, and died in from one to four days. Sixty animals treated with sulfanilamide also died, but the lives of 24 were prolonged for various periods. Monkeys given intracisternal injections of pneumococci died in from twenty-four to thirty hours. Intraspinal injections were not as effectual as oral or subcutaneous administrations. The best results were obtained with a combination of oral administration and subcutaneous and intraspinal injections, although a combination of oral administration and subcutaneous injections appeared to give about as good results as a combination of the three methods. The results indicate that maximum doses of sulfanilamide administered as early as possible may be therapeutically helpful in the treatment of streptococcic meningitis in human beings and is worth trying in the treatment of pneumococcic meningitis.

HUNTER, Philadelphia.

USE OF BENZEDRINE IN THE DEPRESSSED PHASE OF THE PSYCHOTIC STATE. L. A. DUB and L. A. LURIE, Ohio State M. J. **35**:39 (Jan.) 1939.

Dub and Lurie selected for treatment with benzedrine sulfate 48 depressed women patients from a service of about 1,500 patients because of their pronounced depression, as revealed by their mood, speech and actions. The ages ranged from 18 to 75 years. They had been institutionalized for from ten months to twenty-six years. The patients were given 5 mg. of benzedrine sulfate twice a

day. The first dose was given at breakfast and the second with the noon meal. In certain cases the dose was increased to 10 mg. twice a day. This was done if there was no improvement after a week's trial with the smaller dose. The medication was continued for three weeks. A lactose placebo was then substituted without the knowledge of the attendants or patients. The placebo was administered for three weeks, after which no medication was given for two weeks. After this period of rest the patients were again given the placebo for four weeks, after which benzedrine sulfate was again substituted and continued for six weeks. Forty-two women showed definite improvement when benzedrine was administered. Improvement was judged by at least two of the following criteria: weight, cooperativeness and psychomotor activity. During treatment with the placebo, 5 patients became so violent that they could no longer participate in the experiment. Only 5 of the remaining 43 patients maintained their initial improvement, while 38 relapsed when the lactose placebo was substituted for the benzedrine. During the rest period of two weeks, 3 more patients were lost to the experiment, 1 through discharge as apparently cured and 2 because they became violent. Of the rest, 6 remained improved, while 34 remained unimproved. When placebos were again substituted only 3 patients held their gains. In other words, at the end of this period 92 per cent of the patients in this series were practically in the same mental condition as at the beginning of the experiment. But when benzedrine was again administered an immediate and striking improvement was observed in 35, while only 6 failed to respond. An equally striking regression was observed when the benzedrine therapy was again discontinued, the results being practically the same as those during the rest period. The best response was obtained in the paranoid group and patients suffering from cerebral sclerosis, while patients with dementia praecox responded least. The duration of the disease seemed to have no bearing on the results obtained. Age, however, seemed to be of some significance, as the women from 41 to 60 years of age showed the highest incidence of improvement.

J. A. M. A.

THYROID THERAPY IN A SERIES OF EPILEPTICS. G. J. DOOLITTLE, Psychiatric Quart. **13**:33 (Jan.) 1939.

In order to determine the primary effect on seizures and the secondary effects on basal metabolism, blood sugar, weight, tremor, blood pressure and pulse rate, Doolittle gave at first 0.032 Gm. and then 0.065 Gm. of thyroid to 47 patients with epilepsy. During administration the number of attacks increased in 53 per cent of the patients, decreased in 36 per cent and did not change in 10 per cent. In 21 patients the number of seizures increased for the three months after withdrawal of the drug, and 13 of these the number returned to the pretreatment level nine months after withdrawal. An increase in the basal metabolic rate was observed in 91 per cent of the patients, an increase in blood sugar in 63 per cent and a loss of weight in 46 per cent; only 36 per cent showed tremor, and 93 per cent showed a decrease in blood pressure; 84 per cent of the patients in whom a disproportionate fall of diastolic pressure was observed had increased attacks, and 65 per cent showed increase in pulse rate. There seemed to be no relation between the rapidity of the pulse and the number of attacks. About half the patients were receiving phenobarbital. This sedation seemed to have no influence on the frequency of attacks with thyroid. The author believes that improvement with respect to the number of attacks during thyroid treatment was evident in from 35 to 40 per cent of the patients. From 60 to 65 per cent appeared to be made worse by the drug. Approximately the same percentages existed in correlation of seizures with changes in basal metabolic rate, blood sugar, weight, blood pressure or pulse rate and with incidence of tremor. A patient with unstable diastolic blood pressure or a diastolic blood pressure easily decreased by thyroid should not be given this drug.

J. A. M. A.

Muscular System

THE RELATION OF POTASSIUM TO PERIODIC FAMILY PARALYSIS. GEORGE D. GAMMON, J. HAROLD AUSTIN, MARGARET D. BLITHE and C. GRAHAM REID, Am. J. M. Sc. **197**:326 (March) 1939.

In an effort to clarify the relation of potassium to the attacks of weakness in family periodic paralysis, the authors present data in the case of a boy aged 16 in whom the attacks occurred almost daily, invariably in the early morning hours between 3 and 7 a. m., during sleep. During severe spontaneous seizures, the level of serum potassium fell by as much as 30 per cent, and in milder attacks only by from 5 to 10 per cent. Seizures could be induced by water diuresis. There was no evidence of spontaneous potassium diuresis prior to the attack. During the seizure itself the excretion of potassium fell. From 2 to 5 Gm. of potassium chloride by mouth was required to terminate the attacks of weakness. From studies on excretion, it was determined that potassium given during the day was rapidly eliminated, and hence could not prevent nocturnal seizures. It is postulated that the potassium passes from the serum to the disordered muscle in response to an abnormal demand for the metal before an attack. If this is so, the fall in serum potassium is to be viewed as a secondary, or compensatory, decrease. As the attack develops, potassium is drawn from the available sources; when these fail, the serum potassium falls. The more severe the attack the greater is the expected fall in serum potassium.

MICHAELS, Boston.

MUSCULAR DYSTROPHIES WITH HYPOPHYSIAL SYNDROMES. CHARLES RICHET, G. MARANON, ANDRÉ PERGOLA and LOUIS GRAS, Rev. franç. d'endocrinol. **16**:317 (Oct.) 1938.

This is a clinical report dealing with several observations in which combinations of hypophysial syndromes and muscular hypertrophy or atrophy were present. The first case was that of a man aged 71 who had acromegaly and generalized muscular hypertrophy, with increased muscular power. The second case was that of a man aged 51 with signs of acromegaly and atrophy of the Aran-Duchenne type; he had diabetes insipidus, loss of sexual function and loss of all types of sensation in the region of the muscular atrophy. A third patient showed a combination of acromegaly and the Aran-Duchenne type of muscular atrophy; the man presented a syringomyelic type of sensory dissociation. A fourth patient, a man aged 46, had a combination of acromegaly and the Aran-Duchenne type of atrophy. The same combination was observed in a fifth patient, a man aged 70, in whom the condition had developed at the age of 25. The authors report 3 cases of the Fröhlich type of hypopituitarism with muscular dystrophy; 2 of the patients were brothers. In another case generalized muscular atrophy was combined with a tuberohypophysial syndrome. The last case was that of a woman aged 24 with generalized muscular atrophy associated with ovarian insufficiency of hypophysial origin; in this case the genital organs were underdeveloped; there was a Recklinghausen type of cutaneous pigmentation on the back and front of the chest; the patient was mentally deficient.

Biopsies in the cases of acromegaly with muscular hypertrophy showed the usual microscopic picture of muscular hypertrophy. In the cases of generalized atrophy associated with a tuberohypophysial syndrome and in the case of ovarian deficiency there was intense atrophy. The fascicles appeared unequal; there were spaces filled with collagenous material, and the transverse striations were scarcely visible. There were also zones of perivascular leukocytic infiltration, nuclear proliferation and occasional displacement of the nucleus. The transverse sections revealed a volumetric inequality of the fascicles and occasional loss of contour.

NOTKIN, Poughkeepsie, N. Y.

MYOTONIC DYSTROPHY. ERICH KATZENSTEIN, Schweiz. Arch. f. Neurol. u. Psychiat. **42**:249, 1938.

This study was prompted by the finding of myotonic dystrophy with juvenile cataract in 3 siblings and in 3 of their second cousins, who were likewise siblings. A fourth child in the second family had an incipient cataract, but did not have myotonic dystrophy. All the patients were seen at intervals over a period of from four to five years, the presence of lenticular changes being confirmed in each instance by observations with a slit lamp. Information was obtained with regard to 107 members of the family, comprising 7 generations. The majority of the 93 members still living were examined personally. The patients with myotonic dystrophy belonged to the sixth generation; their great-grandfather was born in Württemberg, Germany, in 1818, and the respective paternal grandfathers migrated to Switzerland, where they married.

Five of the patients presented the complete syndrome of myotonic dystrophy, whereas the sixth had only mild myotonia, though presenting generalized dystrophy of high degree. Three of the patients were hindered by the myotonia in earning a livelihood. Muscular atrophy varied somewhat in degree and distribution from one patient to another, the muscles involved being those of facial expression and mastication, the sternocleidomastoid muscles, the small muscles of the hands and feet and the muscles of the forearms and legs. The characteristic thin face and tired expression were pronounced in 5 cases. Atrophy of the musculature of the eyelids was noted in 3 cases, and closure of the lids was weak in another. Atrophy of the soft palate, though rare in myotonic dystrophy, was found in 4 of the cases reported. One patient had difficulty in swallowing. Loss of tendon reflexes was infrequent, but Chvostek's sign was elicited in 5 cases.

Myotonia of the muscles of the hands came on during adolescence or earlier in all of the cases reported by Katzenstein. One patient noticed the symptom as early as the eleventh year, and her sister and brother first experienced it in the fifteenth and seventeenth year, respectively. Contrary to general experience, furthermore, each of these 3 patients showed signs of cataract as early as three years after the onset. Routine use of the slit lamp would probably reveal lenticular changes relatively early in many cases of myotonic dystrophy.

The hair of the head was thin or falling out in 3 cases, and in another the beard was sparse. In all 6 cases there was acrocyanosis; in 1 case slight changes in temperature induced vasospastic phenomena, with marked blanching of the fingers. One patient had small testes, and another, a woman with undeveloped breasts, complained of irregular menstruation. Two patients in the second family had been operated on for goiter; another member who did not have myotonic dystrophy suffered from hyperthyroidism. The patient whose myotonia was of slight degree presented an infantile, dysplastic habitus. In contrast to other members of their respective families, the 6 patients all showed defects of intelligence or personality.

The father of the first 3 patients evidently had mild myotonia, but showed no muscular atrophy, although his hands and fingers were small and he had acrocyanosis. His tendon reflexes were unobtainable, and he had had a cataract in one eye which later had been enucleated because of secondary glaucoma. The great-grandfather of all 6 patients and 2 of his daughters had senile cataracts. The view is expressed that the early appearance of cataracts in the patients with myotonic dystrophy may be an example of anteposition. Contrary to the experience of other observers, the tendency to cataract and myotonic dystrophy was transmitted solely in the male line. Anomalies of the teeth, jaws and palate were frequent, not only in the patients and their immediate relatives but also in collateral lines. The tendency to diseases of the thyroid gland was attributed to the introduction of this tendency into one branch of the family through marriage rather than to the polyglandular disturbance frequently encountered in myotonic dystrophy. No instance of inbreeding could be discovered.

Katzenstein comments on the sudden appearance of myotonic dystrophy in one generation of the family studied and its tendency to appear at approximately the same period of life in all cases. It is assumed that the disease was the expression of a dominant trait which was nevertheless pleiotrophic and therefore tended to express itself in various forms. The author also expresses the view that myotonic dystrophy is not primarily a myopathy or due to an endocrine dysfunction, but that it is the result of changes in the central nervous system, presumably in the vegetative centers.

DANIELS, Denver.

Special Senses

HERPES ZOSTER OPHTHALMICUS. FERDINAND L. P. KOCH, Arch. Ophth. **21**:118 (Jan.) 1939.

Koch reports a case of herpes zoster ophthalmicus in a patient aged 5½ years. The disease affects adults almost exclusively. The treatment consisted of intramuscular injections of whole milk and sedatives. The child recovered without postherpetic neuralgia. Vision was 6/6, and there was no ptosis or damage to the extraocular muscles. The pupil, however, remained dilated and nonreactive, except to mydriatics and miotics, and the cornea was lacking in normal sensitivity.

SPAETH, Philadelphia.

THE PUPILS IN CASES OF CRANIAL TRAUMA AND CEREBRAL TUMORS. EDWARD HARTMANN, Rev. neurol. **69**:647, 1939.

Mydriasis or miosis is frequently seen after fractures of the skull, but they have little prognostic value. When associated with complete immobility of the pupils, they indicate a grave prognosis. The pupils may be of unusual size, in which case the abnormally dilated or contracted pupil is found on the side of the brain which has been traumatized. The pupil may be dilated at first and contract when blood irrupts into the ventricles. Opinion is still divided as to the prognostic and localizing value of anisocoria in cranial trauma. This may be explained by the fact that the size of the pupils changes rapidly. Frequent observation is necessary. Children may react differently from adults. The possibility of concomitant trauma to the orbit or the eye or of traumatic involvement of the oculomotor nerve must be considered in interpreting the data. As to the mechanism of these changes, the following possibilities are suggested: basilar fracture injuring the iridoconstrictor fibers in the oculomotor nerve or the dilator fibers in the semilunar ganglion; compression of these paths by an intracranial hematoma; compression of the cerebral cortex, or diffuse intracranial hypertension. Analogous changes may occur in cases of simple concussion, in which Guillain and Barré suggested a clot compressing the base of the brain, the toxic effect of cerebrospinal fluid containing laked blood or commotion of the eyeball or of the ciliary nerves. In cases of severe penetrating wounds of the brain, mydriasis is almost the rule. In late traumatic sequelae, mydriasis is more frequent than miosis and is usually unilateral. It is more often contralateral than ipsilateral to the side of the trauma. An incomplete Argyll Robertson sign may occur, but should be interpreted with prudence because of its rarity in cases of trauma, the common coexistence of other causes and the lack of unanimity in the definition of the Argyll Robertson sign.

In cases of intracranial tumors mydriasis is more frequent that miosis. Anisocoria seems to have no localizing value clinically, but Adrogué and Balado experimentally produced ipsilateral mydriasis by injections into the ventricles. Isolated abolition of the photomotor reflex of the Argyll Robertson type may be unilateral or bilateral and may vary from day to day and disappear after a decompressive operation. This sign may assist in localizing a tumor compressing or destroying the rostral colliculi, particularly when it is associated with paralysis of the vertical movements of the eyes.

LIBER, New York.

INTRODUCTION TO THE STUDY OF VESTIBULAR DISHARMONY. I. ALFANDARY, Rev. d'oto-neuro-opht. **16**:577 (Nov.) 1938.

The vestibular apparatus occupies an important place in the semeiology of the nervous system. Examination of it is indispensable for the topographic diagnosis of lesions of the cerebral trunk, and the discovery by Barré of vestibular disharmony renders possible the diagnosis of cerebellar lesions, even in the absence of classic cerebellar symptoms. In a harmonious vestibular syndrome all reactions are directed toward the side of the labyrinth excited. However, in certain diseases of the cerebellum or of the brain stem the nystagmus (quick phase) is directed toward the side of the lesion. This phenomenon has been attributed to compression or inflammatory infiltration of the vestibular centers. These hypotheses are supported by experiments and clinical observations, which show that a low bulbar lesion produces homolateral nystagmus, while a lesion at the middle of the bulb causes contralateral nystagmus. Disharmony is a combination of homolateral and contralateral vestibular symptoms, to which is often added the spontaneous, incomplete syndrome: the absence of one of the elements of the vestibular syndrome. In the bulb, the vestibulospinal bundle at a certain level is separated from the vestibular nuclei. and one of them may be affected by a lesion and not the other. In the disharmonious vestibular syndrome these characteristics may be observed: 1. The nystagmus is homolateral; the slow phase is directed toward the side opposite that of the deviation of the trunk and extremities. 2. The deviation of the trunk and extremities is toward the side opposite the irritation. 3. If there is deviation of the head, it is in a direction contrary to that of the other deviations. 4. Deviation during walking is in a direction contrary to the rule. 5. Subjective vertigo is in a direction contrary to the rule.

The author draws the following conclusions: 1. The pure vestibular syndrome is always harmonious, whether the lesion is central or peripheral. 2. The vestibular syndrome becomes disharmonious under the following conditions: (*a*) Lesions of the cerebellum involving the cerebellovestibular pathway; this path is direct and crossed and its function is to coordinate reflex movements destined to maintain the equilibrium of the body. (*b*) Bulbar lesions, either lesion of the vestibulo-oculomotor pathway, which is crossed, or a bilateral lesion of the bulb. In the first instance only the nystagmus is disharmonious; in the second the deviations may also be disharmonious. It is probable that a lesion involving the juxtarestiform body, by disturbance of the same pathways, can produce the same syndrome as a lesion of the cerebellum. (*c*) Peduncular lesions, in which the disharmonious syndrome has not yet been satisfatorily explained. 3. The disharmonious syndrome always indicates a central lesion of the posterior fossa; most often, it indicates a cerebellar lesion. It must be considered a cerebellar symptom of the same value as other cerebellar symptoms of the series of Babinski and André-Thomas, with the reservations already indicated with regard to bulbar lesions.

DENNIS, San Diego, Calif.

Society Transactions

NEW YORK NEUROLOGICAL SOCIETY

CHARLES A. MCKENDREE, M.D., *President, Presiding*

Regular Meeting, Feb. 7, 1939

MODIFIED ROEMER ATROPINE TREATMENT OF PARKINSONISM. DR. LEWIS J. DOSHAY.

The method of administration, the common and unusual reactions and certain results obtained with the atropine treatment in 25 cases of postencephalitic parkinsonism were studied. Each case was investigated by clinical observation, graphic studies and moving pictures before and after treatment. Roemer, of the Hirsau Sanatorium (*Therap. d. Gegenw.* **78**:24 [Jan.] 1937), initiated the massive atropine form of therapy, employing a 0.25 per cent solution in increasing doses. In the present study a 0.5 per cent solution of atropine sulfate was used, because this simplified counting the drops as well as calculation of the amount of the drug.

Method of Administration.—The prescription is simple to write—2½ grains (0.162 Gm.) of atropine sulfate to 1 ounce (30 cc.) of water. A dropper measuring 1 minim (0.062 cc.) per drop is necessary. A half to a full glass of water should be used with each dose. The atropine should be taken at long intervals, 8 a. m., 3 p. m. and 10 p. m. Written instructions should be provided the patient as to the number of drops to start with and the amount and frequency of increase. A slow increase is desirable, particularly in the case of debilitated and hypersensitive patients, in order to establish tolerance. Various safe and slow methods of increase are resorted to, a common practice being to increase by 1 drop three times a day at intervals of three days, until 6 drops are reached, and then to increase at longer intervals and with greater caution up to 10 drops three times a day. Only in exceptional cases is it necessary or desirable to go beyond this dose for any length of time, and one should never go beyond the 15 drop level. In hot weather the dose should be reduced to about half the usual amount, to avoid serious reactions.

Common and Unusual Reactions.—Every patient should be prepared to expect a certain amount of dryness of the mouth and blurring of vision. Nausea and vomiting occur in about 1 of 10 patients, and in such cases the patients should be advised to suspend treatment for a day and recommence with much smaller doses and a slower rate of increase. No serious effects were noted from sudden withdrawal of the drug. Other symptoms consisted of dryness of the nasal cavities, dryness of the fingers, flushing of the face, transient dizziness or lethargy, difficulty in swallowing due to dryness of the throat, loss of appetite, loss of weight and constipation. These symptoms are temporary and never serious and are managed according to the particular requirements of the patient. There was not a single instance of any reaction to cause concern or anxiety.

Results.—Extravagant claims are not made for the atropine treatment, but careful clinical and ergographic studies prove that the drug is of decided usefulness in treatment of the postencephalitic Parkinson syndrome. The action of atropine on skeletal muscles is unknown. Atropine produces mental stimulation and actual physical improvement in many patients. They perform better work, move with greater ease and attend more actively to their personal comforts; they are relieved of distressing pains in muscles and joints as rigidity is lessened; lethargy is diminished; speech is improved as sialorrhea is checked and the buccal and lingual

muscles are relaxed; oculogyric crises are well controlled; mild tremors are benefited, but advanced tremors are unaffected. Supplementary treatments are helpful.

DISCUSSION

DR. JOSEPHINE B. NEAL (by invitation): Dr. Doshay has presented an excellent and conservative consideration of the use of atropine in the treatment of chronic encephalitis. He is especially to be commended on the gradual increase in the dose, the use of amounts of the alkaloid that may be regarded as moderate rather than massive, the decrease in the dose in hot weather and his conservative conclusions in regard to the effect of this treatment. Sir Arthur Hall has a high regard for the use of atropine as a method of symptomatic treatment.

My results with atropine on the whole have been favorable, perhaps not quite as favorable as those reported by Dr. Doshay. I agree with him that it is unfortunate that such exaggerated claims have been made by Roemer, Hays and others. I also agree that the supplementary treatment mentioned by Dr. Doshay is necessary.

For the past nine months my colleagues and I have been trying the so-called Bulgarian treatment on a small group of patients, numbering 60 at present. This treatment consists in the oral administration of a decoction in white wine of the root of the belladonna plant grown in Bulgaria. It may be that the belladonna grown in other countries would yield equally good results. It is known that this decoction contains a number of alkaloids: atropine, hyoscyamine, scopolamine and perhaps others. There is a variation in the amount of alkaloids, and probably in the ratio of the alkaloids contained in the decoction from different lots of the root. Pharmacologic studies should be made to learn what alkaloids are present and what are their relative proportions in the decoction giving the best results. After this is done, it will be possible for standardized preparations to be made. The dose is usually 2 cc. just before retiring, which is increased by 1 cc. daily until the maximum benefit is obtained. As the dose becomes larger it is usually advisable to divide it into two or three portions to be given during the twenty-four hours.

This method of treatment has been extensively used in Italy. The reports of Panegrossi, who is in charge of the work, are extraordinarily favorable.

Our results with the preparation have been better than with any other form of symptomatic treatment that we have used. However, I realize that more patients must be studied over a longer period before definite conclusions can be drawn in regard to the various symptoms that may be improved and the extent and the duration of the improvement.

DR. JOSHUA ROSETT: I wish to ask Dr. Doshay how the atropine and the scopolamine treatment compare. In my opinion, the latter is a satisfactory drug. After hypodermic injection of a suitable dose of scopolamine hydrobromide the tremor and the rigidity are soon notably diminished, without any untoward symptoms following ordinary doses of the drug. I should hesitate to administer the huge dose of 1/4 grain (0.009 Gm.) of atropine sulfate which Dr. Doshay advocates, particularly after he has enumerated the disagreeable symptoms of dizziness, nausea, vomiting and defective accommodation which follow in a number of instances. I did not hear Dr. Doshay say that the improvement in the patients' condition justified the occurrence of the disagreeable symptoms mentioned. What, then, is the advantage of atropine over scopolamine for the relief of parkinsonian symptoms?

DR. GEORGE H. HYSLOP: What interested me most about Dr. Doshay's presentation is the graphic evidence, which speaks for itself, rather than the words of the enthusiastic experimenter. Older pharmacologic textbooks differentiated atropine on the one hand from scopolamine, on the other, as to their action on the central or the peripheral portion of the autonomic nervous system. As I stated in a previous paper (The Treatment of Residual Encephalitis, *J. Neurol. & Psychopath.* **3**:250-261, 1922), my clinical experimental work led me to believe that scopolamine had a more effective action in the relief of rigidity than atropine,

which, according to the knowledge at that time, was primarily effective on the peripheral part of the vegetative apparatus. It is also known that belladonna from different sources varies greatly, not only from season to season but geographically, with respect to the percentage of the various alkaloids which are akin to, or members of, the belladonna or atropine group. That is why I think Dr. Neal is correct in saying that evaluation of the treatment is difficult when one is using preparations which contain mixtures of alkaloids.

DR. HARRY GOLD: Had any of the patients who were treated with atropine with favorable results also been treated with scopolamine in doses larger than they could tolerate? Such a comparison would alone be valid, for they were treated with atropine in doses far above those which patients can tolerate without great distress. If so, what were the results?

DR. LEWIS J. DOSHAY: I am pleased that Dr. Neal discussed the use of belladonna root, with which I have had little personal experience but of which I know something. It should also be understood that the chief agent in belladonna root is atropine. There is little scopolamine in belladonna, and if belladonna root, as well as atropine, is still much in vogue and is still used extensively, it must be that scopolamine, through continued clinical experience, has been found not to be as efficient, as far as the patient's comfort is concerned. When one tests patients by graphic studies after long-continued treatment with scopolamine and various other drugs, and compares the results with those obtained with atropine there is a marked balance in favor of the atropine. Less rigidity and greater spontaneous freedom of movement are produced by atropine than by any other known drug. Some patients have used as many as 10 and more $\frac{1}{100}$ grain (0.6 mg.) tablets of scopolamine a day without obtaining much relief, except for the effect on tremors. The oculogyric spasms and rigidity are helped little by scopolamine, even in large doses. Three or more drops of atropine at night will prevent oculogyric spasms on the following day. Scopolamine does not produce the cerebral stimulation that is obtained with atropine.

PAIN AND THE ACTION OF ANALGESICS. DR. J. D. HARDY (by invitation), DR. H. G. WOLFF and MISS HELEN GOODELL (by invitation).

A CRITIQUE OF TRENDS IN MEDICAL EDUCATION. DR. FOSTER KENNEDY.

My observations on tendencies in the present medical educational system are prompted by my feelings of distress at the advanced age, the wrinkled brows and the sere-and-withered-leaf appearance of those completing their medical undergraduate careers, and at the infantilism imposed through their prolonged sojcurn in the nurseries of the profession. The educational system of today seems, in the schools and in the teaching of the humanities in the universities, to have been sacrificing quality of standards to mere duration.

The ritual of education is devouring youth, without even fattening them first; its prolongation into the late twenties or early thirties must end in the intellectual sterilization of the profession of medicine. Surely it is only in its earliest stages that education can be a matter of factual stuffing. Culture is what is left over when the facts that had been learned have been forgotten. The whole aim of secondary and undergraduate medical education should be directed toward a leading out of the thinking powers of the man or woman. Sound principles, a cultured or scientific outlook, are more important than a store of knowledge. The great mass of the population of any country, biologically speaking, is not educable in terms of the high school if the standard of the high school is high. When one tries to educate in the high school, as is now being done, 70 per cent of American youth of high school age, it must happen that most are not educated at all and the best are not educated enough.

To quote from a bulletin of a great midwestern university for 1938-1939: "The University admits without examination all graduates of high schools in the state which are on the approved list of the Department of Education; a student

who has completed fifteen acceptable units with high grades in an accredited high school may be admitted upon the recommendation of the high school principal." As Gilbert said, "When everybody's somebody, then nobody's anybody."

One hears often that the schools press students, but this is not because the pressure is too great; it is that most of the students are too soft, and should not be there to have the pressure put on them. The reduction of standards in the primary and secondary schools has led, naturally, to a demand for more education in the universities; therefore, too many people go to the universities, where they are taught from the ages of 18 to 22 what they should have learned from 14 to 18. The school system not only should educate as much as is needed for the general population, but should distil brains and produce out of the general mass the best for the higher professions.

It is now twenty-six years since I said here in New York that I could not but feel that American medical education in tying itself to an obligatory degree of Bachelor of Arts before the beginning of the study of medicine had "put its money on the wrong horse." I still hold that opinion, supplemented by a demand for rigorous marking in high school graduating examinations. True, I now know why at that time—more than a quarter of a century ago—the leaders and well wishers of medical education in this country did what they did. For a long time before, a great mass of cheap night schools and medical diploma mills had been debauching the medical profession. It was necessary to use an instrument for their elimination. The instrument best fitted for the purpose then was the classification of medical schools according to certain arbitrary standards; of these standards the most potent weapon, in its effect on medical politics, was the obligatory baccalaureate in the humanities. The result of that policy is known. The weak medical schools were extinguished—indeed for a while to such an extent that hardly enough students were graduated in medicine to deal with the needs of the country. Cults of free thinking, Christian science, naturopathy and osteopathy grew up, largely owing to inability to satisfy the medical requirements of so large a population. However, the obligatory premedical B.A. degree, I believe, has outlived its usefulness, and its ubiquity has led to its degradation. Its existence, so widespread because of lower standards in the schools, has allowed the primary and secondary schools, in vicious cycle, enormously to lower their standards still further. These standards have been lowered, owing to a mistaken idea that education can somehow improve the mind itself. In the nineteenth century it was thought that if one taught everybody everything, one could produce everything from everybody and that by teaching one could make dull minds into bright ones. The advance of biologic knowledge has demonstrated this fallacy and has again made necessary a demand for primary and secondary education adapted to each student's biologic endowment and an educational system which will advance to the highest places persons of the highest minds. A degree in the humanities obtained by factual and durational instruction and not, as was the case in the education of the fathers of this Republic, by competitive discussion; a degree obtained by the collection of credits in courses of oddments, means not education, but only the attainments achieved by agglutination of the tail to a wooden bench, coupled with survival value on the part of the poor dumb animal.

Again, let me repeat that in nearly all places throughout this country students are taught from the ages of 18 to 22 matters which should have been learned between 14 and 18. What is the chronologic result of these four years which must be borne before students can begin the study of medicine? The result is that they begin to study medicine at 22 or 23; they obtain a degree of Doctor of Medicine four years later, at the age of 26 or 27. They have been almost starved of clinical experience during much of this undergraduate period. (The system gets better and better in vitro and worse and worse in vivo, so that the profession has almost ceased to be a learned one and has become instead a union of slick gadgeteers!) So, having finished two years of hospital life, such men as have any drive at all must find themselves caught in some biologic situation of great economic difficulty—a wife, or hope of one—which forbids to most of them any

further pursuit of learning. Further, their most creative, imaginative, fecund decade, that between the ages of 17 and 27, has been regimented, ritualized and given over to the absorption of facts—and how many facts!—when it ought to have been made possible for the good ones among them to have used their good brains for the development of worth while ideas.

Hitler today is living on the human capital of Germany; his placing youngsters in Hitler Youth camps for physical hardening, then in compulsory labor corps, then in army service will make it impossible in the future to mold the product of such a system of sacrifice into an expert chemist, physician or even engineer. Twenty years of this, and Germany will lack leaders and have only laborers. But Hitler is a passing figure, and knows it; he can afford to play ducks and drakes with his human material. The profession of medicine in the United States, however, is a permanent institution and must avoid regimenting and ritualizing, in a manner analogous to his, the youth of the country. Here, I wish to say that I believe that it is uncommon for any man to do work at 40 of which he had not laid the foundation, at least in his thinking, before he was 30. Today one sees in physics and in mathematics the possibility of the world being implemented, and perhaps revolutionized, by men like Dirac, in England, and C. E. Lawrence, in California, at the age of 26.

So far, I have been, you may say, crying like Jeremiah on the roof tops: "Woe, woe, Nineveh!" But surely it is not impossible to improve what I truly think is a most dangerous situation. Instead of the obligatory three or four years of the arts course now demanded before a student can enter a good school of medicine, I should ask that American universities place before their doors a hurdle of some height in the form of an examination, over which if any schoolboy could succeed in leaping he would at once emerge from the chrysalis of school days to the multicolored caterpillar status of a university undergraduate. This examination might be comparable to the matriculation examination, say, of the University of London or the *Abiturium* of the former German universities. For instance, a young man, 16 or 17 years old, might be required to pass an examination comprising, as it might be stated in university calendars: one dead language, including the history of the people who spoke it; one living language, with a reasonable acquaintance with its literature; a large amount of American and annectent history; a general knowledge of world history; all geography; literature written in the English language (I remember that one of my required readings was Washington Irving's "The Sketch Book," but set books are sad fodder; the only way to learn English literature is to wallow in it); the writing of three essays, of at least six pages each, on subjects chosen from six or eight possibilities; all arithmetic; geometry, then, as in my time, all Euclid and original problems arising therefrom; algebra (if it has not been widely dropped by then) as far as the binomial theorem; the principles of elementary biology, and the beginnings of chemistry and physics—as it was called in my time, "heat, light and sound." It should be easy to choose among the candidates in such an examination those qualified to embark on what should be, properly taught, a liberating course of education, a career in undergraduate medicine. Either this should be supplemented by an obligatory first year of the humanities or the subjects that are taught in that first year might well, and I think better, be taught *pari passu* throughout the years of the medical course. I mean that a student of pathology might be a better student of pathology if he were required to read, perhaps, Henry Hallam's "History of the Middle Ages" in the same semester. An appreciation of fine poetry is not incompatible in the same evening with Cecil's "Textbook of Medicine." To have the two running alongside each other might help to diversify thought and stimulate ideas in each field. Nor do I at all want to suggest that the matriculation examination or the *Abiturium* is to my mind ideal. I have spoken only of what I have more personally borne.

Much of the present school curriculum is no more than a vestigial remnant of the past. One is asked to learn to breathe intellectually through gill slits handed to one on a Renaissance platter by a medieval ecclesiastic. It is no longer

necessary, surely, to teach Latin and Greek to every boy every day of every year; I overhead, at 6, my grandfather say, in a domestic controversy, "Let the boy fiddle at it; let the boy fiddle at it," and next morning I heard directly that *mensa* was "a table"! In fact, most of the gerund hunting and Greek particle chasing, with new knowledge knocking at the door each year one lives, is notable waste of effort and time. Surely it suffices if Latin is taught well enough to give each one a sense of the language and if its literature is studied in the great translations.

One may remember here that Benjamin Franklin was given an introduction to Latin for a year at the Boston Latin School at the age of 8, after which he "neglected the language entirely." Years afterward he said he was surprised to find, on looking over a Latin Testament, that he "understood more of that language than he had imagined he would." This encouraged him to apply himself again to the study of it, and he was gratified at his success. If modern experimental psychology has taught anything, it has demonstrated that one cannot learn anything by learning something else. It is often said one must learn Latin and Greek to learn good English, but the best English of the nineteenth century was spoken by Abraham Lincoln, who learned neither; by knowing only four great books, he spoke Stuart English in the grand manner, when every one else talked "hash."

One wonders, too, by how much the intellectual brightness of youth is augmented by their universal application to the Arabic invention of algebra, which, as far as I know, all but one in a thousand promptly forget. The one who remembers is the one who needs it in his daily life.

I think psychology has no place in the high school curriculum, or indeed in any undergraduate arts university course. It gives young people, lacking vital experience, with no standards of comparison to offset the grisly facts of abnormal psychology with which they are confronted, either a completely distorted view of life or, what is worse, an uncertain, insecure and distorted view of themselves. The old discipline of ethics, logic and philosophy might well be revived for the instruction of youth and so-called psychology dispensed with in all school and most undergraduate curriculums.

One sees, therefore, that the terms of the matriculation examination that I have in mind need not be at all those of the past. But they should be high and involve thorough training, so that into the university there goes only the distilled product of the population, in pursuit of higher learning. The responsibility of preparing youth for this discipline would then be thrown, where it properly belongs, on the primary and secondary schools.

Two weeks ago, in an obituary in the *New York Times,* I noticed that a deceased man of distinction "had had only a high school education." I assure you it would be impossible for a Pole or a German of the pre-Hitler period to have spoken in such deprecating terms of having successfully completed his *Gymnasium* experience.

Under these terms, therefore, the student would enter the medical school at the age of 17 or 18 and obtain a licensing degree at 22. Nor do I think that such a man, after such a career, should be dignified by the title of honor of Doctor of Medicine. There is much virtue in higher degrees to act as objectives for further study. Let the young man graduate into the profession with the degree of Bachelor of Medicine, entitling him, should it be necessary under the law, to take his national licensing examination. Two years later he will have completed his general internship, and will have learned at least the elements of his profession and much of its detail. May I repeat that he may not be the worse, at this period of his life, for having carried the humanities up to the portal of his profession and not dropped them into a pit, beside the road, a long way back. Their propinquity, indeed, might breed interest in the daily newspaper, which I find most of the young men only eclectically consider. No earlier than five years after his graduation as a bachelor of medicine would he be permitted to submit an original thesis for the higher degree of Doctor of Medicine. If he is made to compose

an original thesis to this end, he may thereby discover an unsuspected talent in himself. Nor should that thesis, nor indeed any other examination paper, be signed by the candidate or inspected only by his own teachers. Every university surely should have the courage to have its students examined by extern examiners.

All higher degrees, such as F.A.C.S. and F.A.C.P., should be granted only after the completion of a prescribed period of study and instruction and the successful negotiation of an adequate and vigorous examination.

So the doctor of medicine is now 27 or 28. He has completed a general internship, done some original work and probably for three years has been living in a hospital, where particular experience, in matters that especially interest him, is to be had. What now will happen to him must depend, to some extent, on the organization of the medical school through which he has passed. To appraise these matters, one must comment on what is called, for short, nowadays the "full time" system. Academicians will be shocked by the statement that too much anatomy, too much physiology, too much pathology, too much chemistry is being taught to students. It would be impossible for any brain to absorb, much less have time to think about, all the factual material instilled into the undergraduates in medicine. Some method must be found of adapting the teaching in the basic departments to their ultimate objective. For while art is long, there is no way of lengthening life.

No army could hope to wage a successful campaign without a general staff in a position to gather information from all sectors of the front and to coordinate their activities. Such a "general staff" in the medical college should not be entirely medical. In government it is always an error to put a technician in control of a technical department. I should ask such a staff to be composed of 7 men, of whom at least 2 are not trained in medicine but are selected for high office as men of large general intelligence. This board of overseers would listen to lectures, almost as students, and would have the power after discussion with the members of departments to modify curricular material. There is inevitably a tendency in any whole time professor of a great basic science to stand at the door of his cobbler's shop and say: "There is nothing like leather." I have never been present in the lecture room of my colleagues in more than twenty-five years of teaching, nor have I ever seen any of my colleagues in mine. There must be produced liaison officers—with power—to save the hapless student from becoming a supersaturated solution—which, you remember, crystallizes at once into rigidity on the least concussion—of unnecessary, and most forgettable, information. The student today *sua sponte* cries out for more clinical teaching, and he should have it in his undergraduate life in order that, as in the vision of Ezekiel, the bones of science be made to rise up for him clothed with living flesh.

I should like every student from his first year in medicine, and increasingly ever after, to be in the hospital at 9 o'clock for two hours as an assistant to a junior house officer. In my time I was what was called a "pup" to the extern house surgeon or house physician. In my first two years of medicine I became an expert in the treatment of varicose ulcers and an enthusiast in pulling teeth. I learned how to open abscesses, how to bandage and even, with inadequate skill, to set fractures. In the medical outpatient department I could not learn much medicine, but I heard much and learned to recognize the outward and visible aspect of disease. In this way, the foundations of good general medical experience can be laid. It takes many, many years, indeed a lifetime, to become a clinician, and instruction cannot begin too early.

Now, as regards the heads of the clinical departments: Under the influence of the great foundations, the full time professor has become the outward and visible sign of the Intellectual Life. Medicine is science touched by emotion, and without emotion it is a dead thing. So the man who directs one of the great clinical departments should be a man involved in the adventure of life, one able to draw color out of living for the good of his pupils and the growth of his own soul. He should not merely be an inculcator of facts. His lectures should only illuminate facts. If he is a person of fugitive and cloistered virtue he can but

give his pupils stones when they ask for bread. I do not think at all that a professor of medicine should be, as he has been, a part time man, and what I have said shows that I cannot think he should be a full time man. I believe the head of a great clinical department should be a half time man. He would go to the university and hospital at 9 o'clock or thereabouts. He would leave, if he wanted to, about 2 o'clock, and during this period he would not be permitted to write a letter or answer a telephone call regarding his private professional affairs. He would receive not an income of from $15,000 to $30,000 but one of $6,000, $7,000 or $8,000. I believe the kind of man who would accept such an opportunity for, at once, an intellectual life and a life of adventurous independence would do as much for his university, hospital and students in half a day as he would if he had the whole day before him; further, a man of this quality would not take a full time clinical position at any price. Where the idea of the full time position has value and is entirely praiseworthy is in regard to the young man of 26 or 27 who, having completed his resident hospital career and gained the extra decoration of a doctorate in medicine, would obtain by competitive examination a fellowship and instructorship of five years' duration. During these five years, this man, still in the creative period of his life, with a large concentrated experience behind him, freed from economic attrition, would add certainly to the great body of knowledge and, through the creation of his "fellowship" reputation, would be in a position to sail on the stormy seas of professional life when he embarked independently on them.

I have not said much about the methods of medical instruction in general, but the sciences of biochemistry, endocrinology, medical psychology and, as ever, anatomy and physiology must be made more dynamic, more vital, more human; they must be less factual, less rigid and more focused on the objective of medicine than they have been. Twenty years ago, descriptive anatomy and amphibian physiology were all the vogue; much progress has been made since then, but there is still a divorce between the so-called pure sciences and medicine and surgery. The student of physiology should *as such* be familiar with normal heart sounds, with the normal fundus of the eye, with the appearance of the vocal cords in action—he may know the oculomotor nerve of the eye, but what has he seen of convergence, accommodation or pupillary reactions? In short, there should be more physiology in the wards and more humanity in the laboratory and the dissecting room. The normal must be made manifest, handled, seen, recognized, understood, before the abnormal can be appreciated—one must know truth before one recognizes error—and one must know that there is no absolute in either. Truth is hard to find in ethics, but less so in muscles and nerve tracts, and truth in these can be reached if a student studies muscles in action, then dissects them and about the same time is shown them paralyzed by both a lower and an upper motor neuron lesion. The roentgenographic department can be used to supplement physiologic demonstration of digestion and heart mechanisms. The instruments of clinical precision should be familiar and usable long before they are employed to detect the presence of disease.

The ophthalmoscope, the stethoscope, the laryngoscope, the otoscope, the blood pressure apparatus give up physiologic secrets which must be mastered before those of medicine can be comprehended. Cases of neurologic disorders often afford better examples of normal and abnormal function than any animal experiment in a laboratory, and coordinated education can make readily available all such material for students of the basic sciences.

The undergraduate in medicine, then, would have more time in the hospital to learn the difficult art of history taking, the probing of the earliest manifestation of disease; he would grow more easy in the handling of his human charges —he would, in short, be more valuable in the search after first causes of organic disorder and the nature of the psychoneuroses—more able to play his part in the open, mobile warfare of present day medicine and less of a static cataloguing agent in the trench warfare of the past.

In these days of depressed economic conditions it seems proper to close with a protest against the building of medical schools, architecturally up in the clouds and financially down in hell! The outer glorification by brick and mortar causing inner impoverishment of spirit and body! When one looks at Pasteur's laboratory, in the Rue d'Ulm, one sees that minds can leap high from a very small springboard indeed. The replacement of elevation of mind by the elevation of buildings is a disaster; the elevator has become what the French call a waiting room, the place of lost steps. Surely a few of the millions now devoted to the accumulation of corridors could be put to the foundation of large numbers of scholarships, prizes and exhibitions to be obtained in undergraduate life by competitive examination. Surely, too, one could save time by shortening the long vacation, another vestigial remnant of the Middle Ages, when the student had to leave his books to gather the harvest. Now, too often, he is forced to gather his harvest by waiting on Philistines in a summer camp, when, having secured his scholarship, he had better be in the laboratory and wards.

In a single address I cannot seem to have done more than to have seemed fractious and complaining. But whatever I have said comes from more than a quarter of a century of teaching and is freighted with deep sincerity of purpose.

DISCUSSION

Dr. James Ewing (by invitation): I can assure Dr. Kennedy that we have all been entertained and instructed by his philosophic address. Some may have found that old, established ideas of education have been roughly handled, but this is a salutary experience for teachers in university medical schools. In order to digest this address thoroughly, it will be necessary to read it at leisure when it is in print, and I shall not mar that pleasure by a long discussion at present. The ground covered is too extensive. However, some caution will probably be desirable before accepting all Dr. Kennedy's views, for some of the ideas expressed violate certain well established concepts regarding the theory of education.

For instance, I do not think that my four years in college between the ages of 18 and 22 were wasted, and I doubt if I could have profited fully by a college education at a younger period. Three years of study of Latin and Greek under teachers eminent in that field made a strong impression on my mental processes, from which I have greatly profited since. I regret that Dr. Kennedy seems not to have enjoyed association with an inspiring teacher of dead languages.

When a student enters college late and spends four years in medical school and two or three in postgraduate training he enters the practice of medicine very late, and the financial problems then become, of necessity, too predominant in his career. If he marries early the financial problem becomes exceedingly urgent. I wish something could be done to avoid this situation, but I do not see how it can well be accomplished. The directors of secondary schools will doubtless deny vigorously that their standards have been lowered. In fact, these schools have been criticized for demanding too much and for trespassing on the territory of the colleges. The colleges have also trespassed on the field of premedical sciences. I believe it is advantageous for the student of medicine to enter a medical school as soon as he is mature enough to master medical problems. I am not sure that this capacity is often attained before the age of 21.

The requirement of a college degree for entrance on the study of medicine was a method of limiting the number of students. It probably did not raise the standard of preparation or general intelligence, and it fails to work under present conditions. In 1904, Cornell Medical College had 104 students in the entering class, when no degree was required, and in 1905 only 4 students. I did not see then or later any improvement in the capacity or accomplishments of the students. I agree with Dr. Kennedy that some other method of choosing medical students should be devised.

I also agree with him that a full medical degree might well be omitted after four years of study, and that the right to practice medicine should be granted only after proved ability demonstrated in the field of choice. This means more and more

specialization. The boards of medical examiners of the states attest merely to an average general ability of applicants to practice general medicine. In many countries a special examination and license are required to practice any specialty. All these bars tend to extend the period of study and to aggravate the condition of which Dr. Kennedy complains.

The suggestion that the choice of students be limited to the 40 per cent of applicants who are capable of taking a first class medical education is ideal, but until society becomes ideal one may not aim to have a strictly ideal medical profession.

With the second half of the address, dealing with the details of present methods of medical education, the full time system, the details of courses and the introduction of the student into the wards before he is worn out by study of the premedical sciences I fully agree.

I am delighted to find that Dr. Kennedy recommends the appointment of a visiting committee to inspect what is actually going on in the lecture rooms and laboratories of the professors in medical schools. Such a committee might succeed in mitigating the iniquities and modifying the eccentricities of many heads of departments.

Dr. William F. Grady, Montclair, N. J. (by invitation): To attempt to discuss a paper of Dr. Kennedy's is like reaching for the rainbow. I think all will agree with his characterization of what history might call the *"Saturday Evening Post* period" of culture in colleges. In the expression of these opinions he is altogether in line with some of the progressive movements, especially in the Midwest. President Hutchins, of the University of Chicago, has suggested that the B.A. degree be given with the baptismal certificate That is an idea. When one sees the B.A.'s resulting from the summation of hours of sitting at the feet of noted lecturers in neurology and other fields, one wonders whether the kind of mentality that is needed for success in life is to be developed by this type of schooling.

I think President Nicholas Murray Butler made a valuable contribution, many years ago, in his famous book on "The Meaning of Education," pointing out that cultural heritages ought to be incorporated in the curriculums. Educators have put the same things into the curriculums, with little vision or variation, and have been putting the students over the same jumps ever since. The fact is that most of this "cultural" material is really the utilitarian material of the past, the need of which has been outlived. Yet the vested interests of education and the inertia of the human mind are such that there is a tendency to perpetuate not only the identical subjects but the space allotted these subjects in the curriculum. It appears to be inconceivable to think of any course of training in terms of less than four years. As Dr. Kennedy has stated, there were so many books in Euclid, so there must be so many books in the curriculum. The result is that there is created a social condition which is somewhat similar to that which Hitler has capitalized in Europe. Dictatorships have been built on the discontent of young men, and much of this disillusionment arises from the fact that they listen to the promises and predictions of the schoolmasters. Yet these young people go forth to meet only discouragement and disappointment, because they are unable to be self-sustaining economic units.

People in the United States are in the midst of that situation. One should be more practical in the handling of the educational problem, so that at an earlier period there will be developed skills and attitudes that will insure competency in the professional or the nonprofessional field. The traditional academic high schools are typical preprofessional schools for a preferential group, such as those going into the ministry, medicine, law or teaching. Today most of these avenues are blocked, and, furthermore today—and this is not in accord with Dr. Kennedy's point of view—there is the restriction imposed by law that the school required of all the children is not the elementary school but the high school. Pupils may not leave before 16 years of age unless they are graduates of a high school, so that necessity has compelled the rearrangement of secondary schooling, a fact which is well illustrated in the vocational schools developing along various broad lines. It is thought that the best way to meet certain conditions to be faced as a

democracy is to give these children not a generalized education that society will not buy but specific training with a cultural background. In this type of vocational high school there is a six hour day; half of it goes to the traditional cultural subjects and the other half to shopwork, involving creative experience. This type of education brings rich dividends in the form of employment and personal happiness. Such schooling, more than the older academic type, I think, is in line with what Dr. Kennedy advocates. I am confident that there are developed better brains and more critical and more original minds with this modified schooling than with the traditional academic high schools.

May I close with the story of a Greek philosopher who had a rent in his trousers. The Greek tailor, to whom he handed them, looked at him and said, "Euripides." The philosopher looked at him quizically and said, "Eumenides."

DR. EMANUEL D. FRIEDMAN: A few words may be said in support of some of the theses of Dr. Kennedy's provocative address. Dr. Kennedy probably is familiar with some of the newer trends in education. Their aim is to place the superior child in an optimum educational environment, so as to bring out the best in his makeup. I refer to the establishment of so-called country schools in many high schools in New York.

It has also been suggested by some college presidents in America that a secondary degree of associate in arts be granted at the end of the second year of the college career to students who are not capable of reaching the full baccalaureate degree. This is a polite way of stopping further education when it is shown that the students are not capable of carrying as far as some who are better endowed. Of course, the baccalaureate degree cannot give a person anything in the way of native endowment which he has not brought to the college curriculum; if it is demonstrated that the material for steady educational growth is not there, such a person might become a candidate for this secondary degree and then perhaps go on to some vocational school better adapted to meet his potentialities.

With regard to Dr. Kennedy's criticism of the medical schools, may I say that most who teach agree that there should be better integration of the preclinical and clinical sciences, for the structure of medicine grows by the laying of brick on brick, until the whole begins to take form.

One must also be in accord with the notion that the full time clinical teacher is perhaps not the most desirable and effective type. Those who have studied abroad know that in the days of pre-Hitler medicine German clinical training was perhaps the best in the world. It was based on the principle of the half time system; the clinical teacher spent the mornings at the university in consultation with the junior members of his staff who were on a salary and the other half of the day in earning his living. I heard that the late Theodore Janeway maintained that American medicine would make more substantial progress if it would adopt the half time system for clinical teachers similar to that used in Germany prior to the present regime.

Under such an arrangement, instead of a large salary being assigned to a full time clinical chief, considerable sums could be allocated for subsidizing virile young brains and the development of young men who would carry the torch of medicine forward and do it worthily.

DR. FOSTER KENNEDY: I am much obliged to my friends who came here and discussed this paper. Dr. Ewing thinks the secondary school courses have been stiffened. They may have been on paper, but how are they graded? It is possible to stiffen a course, grade the work easily and fail to show the caliber of the student.

It is impossible under a democracy to exclude by decree 60 per cent of students from the schools, but in a democracy one excludes 60 per cent, not on any arbitrary basis but on the ground that they cannot get through. All men are created equal, are they not? Yet when they come to the hurdle 40 per cent get over and 60 per cent do not; they fall out—and that is democracy.

I like Dr. Grady's reference to Hutchins, with his idea that the B.A. degree be conferred with the baptismal certificate; both are apt to be all wet!

I wonder if Dr. Grady knows of Professor Meyer, in London, who is at present the head of the School of Industrial Psychology. It is an important institution, publishing every year a great volume of exercises of what might be called aptitude tests. These aptitude tests have a thoroughness beyond others. Meyer's own brain is so good that the whole school is run on a level of ability and efficiency which should be better known.

I forgot that all students have now to go through high school; this has come about lately as a result of the economic depression and difficulty of adults in getting employment—to prevent children from being employed and to keep them off the streets. I wish to say a word of enormous, of really reverential, appreciation of what this city has done in the way of vocational schools.

CHARLES A. MCKENDREE, M.D., *President, Presiding*

Regular Meeting, April 4, 1939

OBSERVATIONS ON TREATMENT OF MULTIPLE SCLEROSIS. DR. ISRAEL STRAUSS.

DISCUSSION

DR. WILLIAM BIERMAN: It is difficult to state the exact principle involved in production of the profound clinical changes which Dr. Strauss has described following the use of methods that elevate the systemic temperature. There occurs an enormous increase in the velocity of blood flow. There is possibly, therefore, increased vascularization of the regions of the central nervous system that are involved. There is increased permeability of the meninges (Mehrtens, H. G., and Pouppirt, P. S.: Effect of Hyperpyrexia Produced by Baths on Permeability of Meninges, *Proc. Soc. Exper. Biol. & Med.* **26**:287-288 [Jan.] 1929). There is an increase in the leukocyte count, which has been demonstrated to rise from 50 to 100 per cent above the initial count before fever therapy. There occur marked chemical changes and marked alterations in pressure between the vascular system and the fixed cells of the body (Bierman, William, and Fishberg, Ella H.: Some Physiologic Changes During Hyperpyrexia Induced by Physical Means, *J. A. M. A.* **103**:1354-1357 [Nov. 3] 1934). It is possibly by these profound physiologic alterations that one may account for some of the clinical changes to which Dr. Strauss has called attention.

DR. IRVING J. SANDS, Brooklyn: Five or six months ago, Dr. Wechsler discussed fever therapy of multiple sclerosis and cited a series of cases from Mount Sinai Hospital to prove his contention that such treatment of multiple sclerosis not only does no good but is decidedly harmful. I wish to ask Dr. Strauss if he has observed patients who were made worse by this treatment—not during the height of the fever but subsequently.

DR. H. A. RILEY: I wish to ask whether Dr. Strauss carried on any series of control observations in conjunction with the patients receiving hyperthermia.

DR. MARCUS NEUSTAEDTER: Does Dr. Strauss base the improvement on the hyperpyrexia, whether induced electrically or by foreign protein, or on the vitamin B or the arsenic or the haliver oil or on a combination of all these agents? At the Neurological Hospital there are always a considerable number of patients with multiple sclerosis, usually not less than 10; I have tried all these methods and have failed to see improvement from any of them. I am afraid of electrically induced hyperpyrexia; I have had poor results in 2 cases. Some time ago, Osnato and some German neurologists advocated the use of silver arsphenamine. I have tried this in a number of cases in the last fourteen years; in 1 case in particular I had good results. Whether this was due to the silver arsphenamine or to a remission I do not know, but for the past six or seven years the patient has been in fairly good condition in the hospital. A few years ago, Spear, of Baltimore,

reported 12 cases in which he used intravenous injections of a mixture of equal parts of Hartley's broth,[1] the patient's spinal fluid and blood serum of a normal person: he divided 30 cc. of the mixture into five doses, given by injection every other day; he obtained strong reactions and fairly good remissions. I tried this method in 9 cases, in 2 of which the effect on nystagmus was fairly good. In the case of 1 man, who had to be wheeled into the hospital and who could not read, the improvement was so marked that he now walks about with a cane and reads. I have tried quinine for a number of years in all my cases, without noticeable results. It seems to me there is no one particular remedy for all patients; some respond to one and others to something else.

Dr. Strauss should be congratulated on the giving of solution of potassium arsenite U. S. P. over a long period.

Dr. Irving H. Pardee: I am happy to hear that after so many years of neurologic practice Dr. Strauss can still feel enthusiastic about the problem of multiple sclerosis. The cases which he presents are undoubtedly instances of multiple sclerosis; yet I wonder if in many cases a condition which is called multiple sclerosis will not, twenty or more years from now, in the light of further diagnostic knowledge, fit into some other syndrome, and therefore logically responds to the type of therapy which Dr. Strauss has outlined tonight. The whole problem of multiple sclerosis is, unfortunately, a sad one from the point of view of treatment. At least, Dr. Strauss has given a modus operandi which may be effective in some cases. I think that I voice his opinion when I say that, for I am sure that he does not think every patient with multiple sclerosis will respond to foreign protein or fever therapy. Nevertheless, Dr. Strauss's patients have not been observed long enough; the state of the disease five years from now, the type of remissions that will occur, before that time or later, have yet to be reported. I cannot say that my own optimism is greatly raised by Dr. Strauss's report, and yet I am interested in what he says.

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1. Hartley's broth is prepared as follows: One hundred and fifty grams of finely ground beef is mixed with 250 cc. of tap water. The mixture is heated in a steamer to 80 C. To this is added 250 cc. of an 0.8 per cent solution of sodium carbonate, and the whole is heated to 45 C. Five cubic centimeters of chloroform and 5 cc. of Cole S. Onslow's pancreatic extract are added. The mixture is incubated at 37 C. for six hours, during which time it is shaken frequently. Forty cubic centimeters of tenth-normal hydrochloric acid is added, and the mixture is heated in a steamer for thirty minutes. It is then cooled and filtered and adjusted to p_H 8.0 in an S tube. It is sterilized by steaming in an autoclave one hour at 10 pounds (4.5 Kg.) of pressure.

Onslow's pancreatic extract is prepared from fresh pig pancreas free from fat. It is ground fine, and to 100 Gm. are added 300 cc. of distilled water and 100 cc. of absolute alcohol. The mixture is shaken well and allowed to stand at room temperature for three days. It is strained through muslin and then through paper. The filtrate is measured and treated with 1 cc. of concentrated hydrochloric acid for every liter. This causes a cloudy precipitate, which settles out in a few days and can be filtered off. The filtrate keeps indefinitely without an additional antiseptic if it is placed in the ice box in a well stoppered container. If desired for use at once, the filtrate may be used without the addition of the hydrochloric acid, the use of which is to retard the slow autodigestion of the trypsin.

The serum used was prepared after the method of Purves-Stewart; i. e., 10 cc. of spinal fluid was allowed to flow directly into 10 cc. of Hartley's broth. To this was added 10 cc. of the serum of a person, who, as far as could be determined, was free from all diseases. This mixture was incubated for seven days, then inactivated and a preservative added. One to 2 cc. of this serum was injected intravenously once each week.

Five-tenths cubic centimeter of a 5 per cent solution of tricresol was added to 9.5 cc. of the solution.

DR. GEORGE H. HYSLOP: It has long been realized that in this particular syndrome all sorts of things may happen. Years ago, at a meeting of the Association for Research in Nervous and Mental Diseases, Dr. Dana contributed a paper on the ecologic factors in the disease. It is probably common experience that a large proportion of persons with this syndrome have certain morphologic characteristics, that they have also a hypoplastic vascular system; they have a delicate, thin-textured skin; they have blushing of the skin. Attention has been called to the high incidence of the allergic constitution in persons with this syndrome, regardless of its cause. Papers have been published on the influence of lead by Russell, of Montreal, and by Putnam. As a common denominator, there is evidence that the vascular tree is involved. I have been interested in what seems to be the fact that, in addition to the evidence that persons with multiple sclerosis have a certain type of constitution, there is, as Dr. Dana reported, a tendency of multiple sclerosis to occur more frequently in a certain racial stock. This question is based on perhaps an inadequate, but to me, a reasonable suspicion. I have found that when multiple sclerosis occurs in persons of Mediterranean or Alpine stock or in the Jewish race one will find, if not in the patient, at least in the patient's relatives, blue or gray eyes and blond hair. Dr. Strauss's material comes from Mount Sinai Hospital. Have similar observations been made concerning the racial factor?

DR. ISRAEL STRAUSS: I shall answer Dr. Sands first. I have never seen a patient made worse by nonspecific protein therapy. In the 1 case I spoke of, in which I started with hyperthermia under Dr. Bierman's care, the patient had four treatments; because the condition was advancing rapidly I became fearful of the effect of the prolonged hyperthermia, stopped it and changed to the use of typhoid vaccine. Fatalities with hyperthermia have been reported; the supposition is that since the respiratory center is affected one runs a risk in using this method. Therefore I hesitate to employ it if I can achieve what I think is the same result with the use of typhoid vaccine given intravenously. In 1 patient a large quantity of albumin appeared in the urine, and edema was present. Dr. Arthur Fishberg reported that the condition was not nephritis. He said that after the use of foreign proteins intravenously one will occasionally observe such a reaction of the kidneys. The urine after a few weeks became normal, and no albumin has been found since. I have seen no other case in which the symptoms increased or anything unfavorable happened to the patient after treatment.

Dr. Riley asked about controls. The only controls I have are the experiences of many years with multiple sclerosis. I have not treated one group of patients and left another group untreated for comparison. To carry out such a procedure in a proper manner is almost impossible; even if it were done, the facts obtained would be unreliable because of the great variance in symptoms which the disease exhibits. A study has been carried out by the American Neurological Association for many years; but a study of this disease requires careful examination and tabulation of every symptom by neurologists, and it means a summing-up of each case which one cannot do on paper. I have refused to treat patients with advanced disseminated sclerosis by this method because I think I cannot accomplish anything by this, or possibly by any other method. A patient who had had multiple sclerosis for many years was carried in because he could not walk. I did not want to give typhoid therapy, but Dr. Globus, who had sent the patient in, requested it. After treatment the patient walked out of the hospital. I do no know how long he maintained the power in his legs, and I should not be surprised if the condition recurred, because the condition was one of years' standing.

It is difficult to evaluate improvement scientifically, so that the only standard is one's own opinion as to whether or not a patient has been helped. I believe that patients with the early stage of the disease, including those with transient diplopia for several years or a temporary scotoma for two or three years previously, who show no marked objective evidence of the disease, are most amenable to treatment. Whether one is successful is another question. Of course, I do not claim any cure.

Dr. Neustaedter says he is delighted to hear I use solution of potassium arsenite. Older neurologists remember the time when arsenic was used in many cases of

the chronic form, with some favorable results. For a long time I used sulfarsphenamine in cases of multiple sclerosis and postencephalitic paralysis agitans, and discontinued it only after I had seen a case of fatal arsphenamine encephalitis.

As Dr. Pardee said, in time I may find that these patients have outspoken multiple sclerosis. I dare say that in several years the disease process may have advanced. Perhaps four or five years hence I can report on these patients, and if they are as they are today, or only slightly worse, Dr. Pardee will still be skeptical and say: "Do you think it is your treatment which has achieved the result?" I shall say: "I know only that under the regimen I have prescribed the *status quo* has been maintained." Perhaps it is true that the multiple sclerosis is a "wastebasket" for the diagnosis of other conditions. Some time one may find that included under this diagnosis are cases which can be segregated and which are not those of multiple sclerosis, but at present one must use the criteria available.

Dr. Hyslop has asked an interesting question. I have not studied the cases of multiple sclerosis from the point of view of a constitutional predisposition, but I agree that there is unquestionably such an element. It is true that Jews are frequently afflicted with multiple sclerosis. I do not know how much there is elsewhere; I do not know whether the Alpine peoples have certain characteristics which make them more susceptible to the disease, but I believe that there is a constitutional factor which makes one person more susceptible to the disease than another; whether it is the type with blond hair and blue eyes I do not know.

ADIE'S SYNDROME: REPORT OF THREE CASES. DRS. JOHN MCDOWELL MCKINNEY and MAURICE FROCHT (by invitation).

Three cases of Adie's syndrome were presented, with a moving picture demonstration of the characteristic signs.

CASE 1.—A married white woman aged 32 showed a dilated right pupil, which was fixed to light but gave the typical tonic reaction in accommodation. The deep reflexes were normal.

CASE 2.—A married white woman aged 28 had a dilated left pupil which did not react to light, but showed the typical myotonic reaction in accommodation; the left ankle jerk was absent. She also suffered from convulsive seizures, diagnosed at the Neurological Institute of New York as idiopathic grand and petit mal epilepsy.

CASE 3.—A Puerto Rican man aged 51 presented a dilated right pupil which did not react to light or in accommodation and absence of the right ankle jerk.

In summary, while nothing definite has been proved, the facts so far elicited make the following statement tenable: Adie's syndrome is a disease *sui generis*. It runs a chronic and benign course and may exist either alone or in conjunction with other diseases. It is perhaps heredodegenerative, but is not syphilitic.

DISCUSSION

DR. W. GUERNSEY FREY (by invitation): Whatever ophthalmologists know about this condition they owe to neurologists. Until Dr. Foster Kennedy and his associates called Adie's syndrome to the attention of the local ophthalmologists at a meeting of the Section of Ophthalmology of the New York Academy of Medicine on Oct. 18, 1937 (Adie's Syndrome, *Arch. Ophth.* **19**:68 [Jan.]; 838 [May] 1938), it was a virtually unknown entity to practically all of them. As a demonstration of this attitude, a member of the New York Ophthalmological Society had presented the first patient to that body several years previously as an interesting case of anomalous pupillary reactions; none of the ophthalmologists who saw her were able to diagnose the condition. Subsequently, when she came to my service at St. Luke's Hospital, with Dr. Kennedy's paper in mind, I referred her to Dr. McKinney as probably having Adie's syndrome.

The pupillary reaction in the one eye of the first patient seems to be typical of the case of this syndrome. The left pupil reacted normally to all tests. The right pupil generally appeared larger than the left and did not react, either directly or consensually, to ordinary tests for the light reflex. The reaction to accommodation and convergence, however, was fairly prompt, and the pupil returned to a size approximately equal to that of the fellow eye. Moreover, when the patient was placed in the dark for a time the right pupil dilated slightly more than the left, and this secondary dilatation was overcome on return to the light. Reactions to the various miotic and mydriatic drugs were not disturbed. Light thrown into the dilated right pupil caused a consensual reflex contraction of the pupil of the opposite eye. General physical examination and special tests made on this patient offered no etiologic explanation—she was not syphilitic, and investigation failed to bring to light any similar phenomenon in other members of her family.

I shall not be so bold as to hazard a guess or offer a hypothesis to explain the physiologic or pathologic basis of these unusual pupillary reactions. It is perplexing, however, to find grouped under one general heading a number of pupillary reactions which are at least superficially dissimilar, as illustrated by cases presented here tonight and those on which Dr. Kennedy's paper was based—a dilated pupil which is fixed to light but does react in accommodation, a contracted pupil which is fixed to light but does react in accommodation; a dilated fixed pupil, a contracted fixed pupil.

I agree with Dr. McKinney that it may be wise, for the sake of clarity, to restrict the diagnosis of Adie's syndrome to typical cases in which a pupil is generally dilated, does not respond to ordinary light stimulation (but may after secondary dilatation has been induced by the patient's being in the dark), and does react in accommodation and convergence.

Dr. H. A. Riley: I have nothing to add to the discussion of this situation. I saw the second patient whose case Dr. McKinney reported. There is, as Dr. McKinney has said, no explanation, so far as a common denominator is concerned, for the linking of the two clinical features in this syndrome, and I can conceive of no explanation for the association of these two rather widely separated clinical facts—the change in the pupil and the loss or diminution of the ankle jerks. I wish to thank Dr. McKinney for having brought this again to our attention. These situations need to be recalled periodically; otherwise, one is likely to forget them and not to look for these rather unusual and seldom seen phenomena.

I wish also to congratulate Dr. Frocht on his photographs. It is difficult to show alterations in the size and reaction of the pupil—I know, because I myself have tried to photograph them—the pictures are as satisfactory as they can be.

Uremia: A Neurohistologic Study. Dr. Jacob H. Friedman (by invitation) and Dr. Mark G. Kanzer (by invitation).

In view of the neurologic and mental symptoms in uremia, pathologic studies of the central nervous system have been made, but have thus far failed to yield satisfactory data. Older writers confused cases of hypertension, eclampsia and arteriosclerosis with those of uremia. Recent writers, within the past decade, have also confused the issue through lack of agreement as to the pathologic changes. Textbooks have vague and varied neurohistologic descriptions of the brain in uremia.

We have reinvestigated this problem and have studied the cerebral cortex, striate bodies, brain stem and cerebellum in 12 cases in which death was caused by uremia. The brains in 7 cases of uremia and suburemia and in 15 cases of nonuremic disease (cardiac disease, pneumonia, sepsis, cirrhosis of the liver, arteriosclerosis, meningitis, atelectasis and abscess of the brain and 4 normal brains were studied with special regard to the xanthydrol stain, as used by Oestreicher, who expressed the belief that this reaction is useful in establishing the diagnosis of uremia by means of the crystals precipitated in the brain tissue.

Our conclusions are as follows: 1. In uremia, the constant neurohistologic changes are (1) generalized astrocytosis; (2) degeneration of the cortical nerve

cells, with less severe similar changes in the striate bodies and brain stem, and (3) thickened and edematous leptomeninges.

2. The brain tissue undergoes alterations in uremia, as it does in the presence of a toxic agent acting over a long period.

3. The xanthydrol stain is not specific, and hence is not diagnostic of uremia.

4. No correlation between the clinical findings and the neurohistologic features in uremia can be shown, beyond the fact that a rather widespread toxic degenerative encephalopathy is commonly seen.

DISCUSSION

DR. JOSEPH H. GLOBUS: I sense a certain disappointment—not with the demonstration, which was excellent—but with the paucity of the changes observed in the study. One would expect with this evidence of massive neurologic involvement to find more morphologic disturbance in the nervous system. One definite point was brought out: The glial mechanism has reacted to some toxic material circulating through the nervous system. That in itself is important. The facts that there was no evidence of vascular change, that there was no massive destruction of nerve tissue and that there was no evidence of demyelination are exceedingly important, because they immediately rule out vascular disease as responsible for the morphologic and physiologic disturbance in the nervous system as part of the syndrome of uremia. The only alteration which could be readily visualized was the increase in the glial elements. But this increase was more apparent than actual. The fact that glia cells were more prominent and more easily recognizable in the preparations demonstrated does not mean that the glia cells were actually present in greater number. I think they were larger rather than more numerous. Their prominence was due to the increase in size of the individual glia cell rather than to an increase in the number of glial elements. The fact that they were increased in size is, of course, a pathologic manifestation. Dr. Friedman has pointed out, and this is probably correct, that the enlargement of the glia cells is due to absorption of toxic material, a process essential to protection against the noxious effects of the toxin of the more important nerve elements. I believe that this paper, if it does nothing else, demonstrates that the astrocytes are important structures in defending the more important, more physiologically significant cells of the nervous system. Occasionally, when the toxic material was present in too large amounts, when the glia cells were unable completely to defend the adjacent nerve structures, nerve cells received some of the toxin and succumbed. There is a strong probability that the number of nerve cells was reduced; certainly, some of the nerve cells showed evidences of early disintegration.

DR. LEWIS D. STEVENSON: I had the same difficulty in demonstrating anything satisfactory in cases of uremia which I studied. The reaction shown here is what one could find with any toxin circulating in the brain. Similar changes are seen in the brain in cases of chronic alcoholism. One sees the thickened arachnoid, which I have come to regard as due to a toxin circulating in the brain, and the reaction on the part of the glia. In the first slide shown by Dr. Kanzer, I regard the glial reaction as due largely to the oligodendroglia; the nuclei seemed to have a halo around them and did not look like astrocytes. The reaction of the astrocytes I should regard as due to loss of nerve cells and an attempt to replace them. The concept of the astrocytes as protecting the nerve cell is new to me. I believe that the oligodendroglia cells have such a function because one sees evidence of it around the nerve cells normally, and when an insult is offered to the brain these cells seem to surround the nerve cell in a protective capacity. I think the sections show merely the effects of a toxin circulating in the brain for some time.

DR. JOSEPH H. GLOBUS: I am glad that Dr. Stevenson raised the question of the importance of the astrocytes as defense elements. I think he accepts fully the concept that the oligodendroglia and the microglia cells are the only glial elements which are concerned with defense of the nervous system. However, I am sure that he will agree with me that one finds astrocytes in increased numbers and in

increased size in areas in which no destruction has taken place, for instance, in the proximity of tumors. One often sees increase in the glial elements, particularly of the astrocyte variety, which extends over wide areas where no destruction has taken place and there is alteration only in the nutritional function of the tissue. One finds gliosis in cases of alcoholism and of any other toxic change in the brain in which no massive or circumscribed loss of tissue has taken place. The striking thing in these cases of uremia was the lack of evidence of localized small or large areas of loss of brain tissue. There was no need for actual repair. There was no need for scar formation. The glia cells were present in areas in which there was no frank evidence of disease, except as marked by their own presence. It will also be noted frequently that the astrocytes are filled with fat, and the question has often been raised whether astrocytes are not capable of giving rise to compound granular corpuscles. The material in this group of cases would point to the possibility that astrocytes have phagocytic potencies.

NEW YORK NEUROLOGICAL SOCIETY AND NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

Joint Meeting, March 7, 1939

CHARLES A. MCKENDREE, M.D., *President of the New York Neurologic Society, Presiding*

A CASE OF COLLOID TUMOR OF THE THIRD VENTRICLE AND CONCOMITANT LARGE SELLA TURCICA, WITH NECROPSY OBSERVATIONS. DR. M. NEUSTAEDTER and DR. THEODORE MELTZER (by invitation).

Cases of colloid tumor of the third ventricle have been reported from time to time. Except for such symptoms as headache, vomiting, papilledema and mental phenomena, which one finds associated with tumor of the brain, there are no characteristic symptoms of a tumor of the third ventricle. Ventriculograms may be of localizing value. The interest of this case lies in the fact that neither symptoms, which were obscured by the presence of a large sella turcica, nor encephalograms were of any assistance.

Clinical History.—H. C., a man aged 46, was admitted to the hospital of the Neurological Institute on June 11, 1938. In October 1934 the patient first began to suffer from constant headaches and urgency to micturate. A urethral prostatic resection was performed in 1936, but afforded no relief. After that operation he was subject to convulsive seizures, of very short duration. During one of these attacks he sustained a fracture of the right forearm. The character and frequency of these seizures could not be determined. The headaches increased in severity, and the patient became lazy. He was admitted to a hospital, where he was told he had a tumor of the brain, and was discharged after four months' stay. After his discharge his libido increased considerably and became objectionable to his wife. She complained that he had become boisterous and facetious and had him committed to a hospital for mental disease. From there he was soon transferred to a general hospital for neurologic investigation, and from there to another hospital, where a diagnosis of adenoma of the pituitary gland was made. He received roentgen therapy during March and April 1937. At this time the Janney test on the urine yielded 240 mg. of sugar per hundred cubic centimeters in the fifth specimen; the visual fields showed generalized, slight contraction, and the upper quadrants of the disks were blurred. After irradiation he constantly gained weight; by the end of 1937 he had gained 24 pounds (10.9 Kg.), but had become

generally weaker and suffered from retention of urine and feces. At this time he became more drowsy and irritable and showed impairment of memory, but he no longer complained of headache or visual disturbances; on readmission to the same hospital, on Dec. 30, 1937, he was confused and irritable and at times somnolent. Examination showed acromegalic features, a tendency to greasy, masklike facies, female distribution of hair and glycosuria, with a sugar content of 1.4 mg. per hundred cubic centimeters. The basal metabolic rate was minus 4 per cent. The chemical constituents and serologic reactions of the blood were normal. Roentgen examination of the skull showed marked enlargement of the sella turcica, with decalcification and thinning of the dorsum and the posterior clinoid processes.

The patient entered the New York City Cancer Institute Hospital on May 25, 1938 for further roentgen therapy; here he was seen by us and transferred to the Neurological Hospital for further observation.

The past and family histories were essentially unimportant.

Physical Examination.—The pupils were equal but irregular and responded sluggishly to light and promptly in accommodation. The vessels of the fundi were injected; there was slight bilateral papilledema. There was a questionable Hoffmann sign on the left; the abdominal and cremasteric reflexes were absent; all other superficial and deep reflexes were present and more active on the right side; there were an unsustained ankle clonus on the left and a wrist clonus on the right, but no other pathologic reflexes. Sensibility was intact throughout. Motor power was normal. Anosmia to coffee was present on the left side and to onions on both sides, and there was considerable hemianopia bilaterally.

On June 7, 115 cc. of air was insufflated in 5 cc. quantities after the removal of 111 cc. of spinal fluid, the initial pressure being 18 mm. of mercury. On roentgen examination there appeared no filling of the ventricular system; none of the air was delineated within the cranial cavity. Seven days later additional encephalograms showed marked bilateral internal hydrocephalus. The laboratory findings were normal.

Course.—The patient's condition remained unchanged. On June 12 he suddenly became semicomatose. He did not respond to questions, but only to painful stimuli. Examination revealed increase of the papilledema, bilateral wrist clonus and a Hoffmann sign, and equivocal Babinski and confirmatory signs on the right side. Throughout the examination there were clonic twitchings of both upper extremities. The patient remained in this state for two days. A neurosurgeon considered his condition too serious for craniotomy. The right lateral ventricle was tapped with the intent to remove some of the air which obviously had not been absorbed. However, the patient did not respond, and died on June 16.

Autopsy.—Grossly, the pituitary body showed no enlargement superiorly. The posterior clinoid processes were eroded. The sella turcica measured 2 cm. Coronal sections disclosed a tumor of the third ventricle, 1.5 by 2.5 cm. There was bilateral internal hydrocephalus.

Microscopically, the tumor consisted of a colloid cyst surrounded by a fibrous membrane, in which there were blood vessels and numerous ependyma-lined cavities. The cells of the pituitary body were qualitatively and quantitatively fairly normal, but the blood vessels showed marked congestion and the central portions and interspaces of the acini were enlarged.

Comment.—The characteristics of colloid tumor of the third ventricle are definite. The growth is benign, obstructs the foramens and produces internal hydrocephalus. The tumor, as it enlarges still further, tends to fill the third ventricle and to press on the structures bordering on this cavity, and produces symptoms of diencephalic and extrapyramidal involvements. The fact that this tumor is a midline structure and grows neither to one side nor to the other, but tends rather to distend the third ventricle, accounts for the lack of lateralizing signs of motor or sensory nature. Its close proximity to the fornix leads one to believe that obstruction to the fibers of the rhinencephalic system, as they stream from

the hippocampal gyrus to the corpora mamillaria, would lead to disturbance in the sense of smell, as was evident in our case; anosmia has infrequently been reported in the literature.

The nature and development of the colloid tumor have been the subject of considerable discussion. The tumor has at various times been called: (1) cyst of the choroid plexus; (2) degenerated glioma; (3) degenerated sarcoma; (4) ependymal tumor; (5) cystic tumor of the septum pellucidum; (6) neuroepithelial tumor or cyst, and (7) paraphysial cyst.

It is generally conceded that this tumor represents a developmental defect—a remnant of a vestigial organ, namely, the paraphysis. A clearcut distinction is made between this tumor and a true cyst of the choroid plexus in that in the latter the cuboidal epithelium lies on the outside of the cyst, whereas in the colloid tumor the cuboidal cells lie on the inside. This view appears to be in accordance with the development of the paraphysis and the choroid plexus. The choroid plexus is, in the last analysis, a core of vascular connective tissue (an extension or inclusion from the primitive pia-arachnoid covering the hemispheres) covered by a layer of ependymal cells. Since the paraphysis is an evagination of the primitive cerebral vesicle, such evaginations must have the ependymal cells as an internal layer, and this is evidence that the colloid tumor is derived from paraphysial evaginations which have, instead of disappearing during the normal course of development, become occluded with the formation of a cyst, which, becoming distended with secretions from the lining cells, grows larger until it causes clinical symptoms by its interference with the circulation of the cerebrospinal fluid.

DISCUSSION

DR. JOSEPH H. GLOBUS: I have had some experience with this case, since the patient was admitted to the Mount Sinai Hospital; hence I may add something to the clinical picture and perhaps explain why the tumor was not approached surgically and why there was no diagnosis. When the patient was first admitted to the hospital a striking feature was the absence of localizing signs. Signs pointing to hypothalamic or diencephalic involvement were exceedingly meager and speculative. On the other hand, there was direct evidence that the sella turcica was markedly enlarged and the clinoid processes partially calcified, and there was ample evidence for the assumption that the patient had a tumor of the pituitary gland—a pituitary adenoma. He was treated for this and, strangely, responded to the treatment; this favorable response further crystallized the idea that the tumor was adenomatous and was attacking the pituitary itself. The patient left the hospital and returned several months later to the follow-up clinic, where he reported further improvement—additional proof that the diagnosis was correct. Shortly afterward, he returned; this time he reported having intense headache, somnolence and certain peculiarities in conduct. He was therefore readmitted to the hospital. At this time the resident made an important observation. He noticed the pathologic changes—the emotional alterations—but he also observed that there was evidence of hypothalamic disturbance, that there were involvement of the pyramidal tract on one side and some parkinsonian features; this led him to assume that there must have been involvement of the hypothalamic region. He recommended that a ventriculographic, not an encephalographic, examination be carried out, for, with the suspicion of a tumor of the third ventricle, he judged that the encephalographic procedure would not be safe. The patient began to improve, but Dr. Israel Strauss, then chief of the service, was uneasy about the diagnosis in view of the high readings for cerebrospinal fluid pressure, and was inclined to the diagnosis of a tumor in the third ventricle. However, he was overruled by other observers, who claimed that there was improvement and that this was direct evidence of the intrasellar disturbance of the pituitary. It is significant that the roentgenologist who reported enlargement of the sella turcica called attention to the fact that changes in the sella might be secondary to internal hydrocephalus. Throughout the study of the case at the hospital there was always the suspicion

that the patient had a tumor of the third ventricle; however, the large sella turcica and the favorable response to roentgen therapy discouraged surgical approach at that time. Encephalographic examination was made elsewhere, and, strangely, air, which was not in evidence at first, appeared later and was retained in the ventricles for an unusually long period. I cannot offer an explanation for this, except that with the complete obstruction of the third ventricle the escape of air into the subarachnoid space was blocked; this may have been the cause of the poor absorption of air. It is also probable that the ependymal lining of the ventricles was so disturbed that it did not contribute its share to absorption of the air. Still, I do not understand why the ventricles should have failed to fill at the time that air was injected and why air should have appeared in the ventricles, to be retained for such a long time. However, I am not called on to explain that. I suppose Dr. Neustaedter and Dr. Meltzer have an explanation.

As to the character of the tumor: As I looked at the projected pictures, my impression was that the wall of the cyst contains a good duplicate of the subependymal structures; the small alveoli, the small glands, three or four rows of them, are reproductions of the embryonic ependymal, cystlike structures which one sees in the embryonic brain. If this is correct, one may trace its origin, as Dr. Stookey and others are inclined to do in the case of similar cysts, to the possibility that the colloid cyst is ependymal in origin; when one realizes, however, that the paraphysial pouch is also mainly ependymal in origin, forming in part the roof of the third ventricle (and as such it is in part ependymal in character), it is of purely academic significance whether the tumor is derived from the paraphysial pouch or from the adjacent ependymal lining. Before I saw these structures I was inclined to believe that most colloid tumors are paraphysial in origin because of the uniformity in their location and the structure of their walls, as well as for other reasons, but now I am somewhat uncertain. Perhaps it is best to consider some as paraphysial in origin and others as ependymal, depending on the histologic structure of their walls.

Dr. Byron P. Stookey: This patient presented a combination of symptoms of pituitary disturbance and obstructive hydrocephalus as a result of the colloid cyst. I do not see how the problem could have been solved without air studies. I think it would not have been possible to do so on a clinical basis. Certainly, in no case of colloid cyst that I have seen has the pituitary fossa been eroded as this one has been; it seems to me, in fact, that this patient had both a pituitary tumor and a colloid cyst. I wish to subscribe to what Dr. Globus said about the dangers of injection of air. In cases of this type injection of air presents a tremendously grave risk, and I believe the patient must be followed and the background laid for an immediate operation after the diagnosis is established.

As to the operation itself, I do not know of any group of cases in which the outlook for complete surgical cure is better if the diagnosis can be established and the patient brought to the operating room in a satisfactory condition. The tumor usually can be removed completely. The only difficulty I have encountered has been in 1 instance in which approach had to be made through the right frontal pole; there was extensive scar formation at the site of incision into the pole, with subsequent adhesion of the frontal lobe to the dura and the development of convulsive seizures.

Dr. Marcus Neustaedter: I had the patient under observation for a few days only. The only explanation I have for the hydrocephalus becoming evident later in the air studies is the possibility that the fluid seeped out and the air entered the ventricles, owing to a change at times in the position of the tumor, since it was attached by a pedicle. I had in mind a tumor of the third ventricle because I tested the patient by a sign to which I referred several years ago, as did also Dr. Wechsler, I believe. He made the statement that when patients with such tumors shake their heads they become dizzy and faint. I shook this patient's head vigorously, and he did not become dizzy or faint. The reason I did not retain the possible diagnosis of tumor of the third ventricle was that the patient

had repeatedly been at the Mount Sinai Hospital, where the enlarged sella turcica and the signs of pituitary dysfunction were observed, and I felt that the diagnosis was confirmed. When it was suggested that the neurosurgeon should operate, the patient's condition was such that he was a poor operative risk, and the only thing to do was to evacuate some of the air from the ventricles through a trephine opening.

OBSERVATIONS BASED ON ELECTRICAL STIMULATION WHICH INDICATE THAT IN MAN PRIMARY CENTERS FOR MOVEMENTS OF THE UPPER LIMB EXTEND UPWARD ON THE LATERAL SURFACE OF THE CEREBRAL HEMISPHERE AS FAR AS THE SUPERIOR MESIAL BORDER, AND THAT PRIMARY CENTERS FOR MOVEMENTS OF THE LOWER LIMB ARE RESTRICTED TO THE MESIAL SURFACE OF THE CEREBRUM. DR. JOHN E. SCARFF.

I believe that in man the so-called motor cortex has migrated to a higher position on the lateral convexity of the cerebral hemisphere than it occupies in any of the other primates, so that as a rule the centers for primary movements of the upper extremity extend up to the superior margin of the hemisphere, while in most instances the lower extremity is entirely unrepresented on the lateral surface of the cerebrum.

In support of this view, 15 cases are reported in which the superior mesial border of the hemisphere was exposed at operation and stimulated electrically. In all but 1 of the cases the cortical representation of the upper extremity was found to extend to the midline, the center for movements of the shoulder being located at the superior mesial border. In none of the 15 cases, with the single exception noted, were centers for primary movements of the lower extremity found on the lateral convexity of the hemisphere. The exception to this general rule was the case of a small Negro boy. In 2 cases focal contractions of the rectal sphincter were obtained, without other muscular movements, as a result of stimulating the mesial surface of the hemisphere in the region of the sulcus cinguli.

DISCUSSION

DR. FOSTER KENNEDY: This is really, I think, a study in phylogenesis. When a superior water creature came out of the sea and climbed, by reason of need, onto the land, the first thing it had to do, in order to exist, was to breathe. The next thing was to move, and in the lower creatures the lower part of the motor area is for the leg. In the phylogenetic advance there is a neurotactic elevation of the leg-representing area. The first thing that was necessary was movement. The last thing which was necessary was speech. As the animal ascended in the scale, the representation of movement proportionately advanced upward until, as Dr. Scarff has shown, it finally "went over the top." It is interesting to see that this idea of the representation of leg movement as being "over the top" has been largely missed, owing to the fact that the surgeon had to avoid the longitudinal sinus. Also, the error shows human capacity for making a pattern; one likes to make a diagram in order to make things clear, and one overdoes the clarity. Therefore, examination of the pictures and the textbooks since about 1870 shows that every man copied other men's pictures, but that every man set his own text and that the text beside the pictures in no way interprets them. One has to read the text in order to find the particular experimenter's results because the pictures with which he illustrates them do not do so. This is not a unique example; similar situations occur in almost all physiology—a tendency to "pinch" pictures and to save trouble. Dr. Scarff has done an important thing in showing the fallacy of the illustrations to which one has become accustomed and in demonstrating where the true center lies: over the top of the great fissure.

DR. BYRON P. STOOKEY: This is an important contribution. First, to the clinician localization of the arm and shoulder areas is of great importance, and heretofore it has been considered as much lower. Second, I pay tribute to Dr.

Scarff for calling attention to the fact, as Dr. Kennedy has said, that people have transposed into the textbooks diagrams of the chimpanzee's brain and the localization which belongs to it, and have taught that as the localization in the human brain. Dr. Scarff is the first to call attention to the fact that in the textbooks the leg area appears in a place that one now recognizes to be the shoulder area. I think this is a brilliant and important contribution.

DR. JOSEPH E. J. KING: I wish to reiterate every word that Dr. Stookey has spoken. This is one of the finest pieces of clinical work that has been done in New York and presented before this group. I feel sure that surgeons have believed that the arm, hand, shoulder and face areas were much lower than Dr. Scarff has shown tonight; by comparing one case with another he has demonstrated exactly where these areas are and has proved the fallacy of the old teaching.

FRONTAL LOBECTOMY IN TREATMENT OF TUMORS IN THE ANTERIOR CRANIAL FOSSA. DR. BYRON STOOKEY, DR. JOHN E. SCARFF and DR. M. H. TEITELBAUM, Brooklyn (by invitation).

Block removal of large parts of the frontal lobes for neoplasms or traumatic epilepsy furnishes an approach to the study of the so-called silent areas, supplementing the purely clinical and experimental observations which have been made in the past. Up to the present, however, only a few cases have been recorded in which a critical study has been made of the effects of lobectomy (Penfield and Evans; German and Fox; Spurling).

Lobectomy was performed in 23 cases for a glioma of the frontal lobe, for traumatic epilepsy or for a large subfrontal tumor that was otherwise inaccessible. Sixteen of these in which the lesion was completely removed were studied critically and are reported by us. In 9 cases the dominant and in 7 the nondominant lobe was removed, but no special difference between the two groups was observed. Four cases in which the lesion was incompletely removed were discussed briefly.

In this series of cases the incision as a rule included areas 8, 9, 10, 11, 32, 34, 46 and 47, and occasionally 6 ab. When the lesion was completely removed, little or no impairment of intellectual function resulted; emotional and social adjustments were satisfactory, and there was no loss of inhibition or spatial orientation. Incomplete removal, on the other hand, was followed by emotional instability, listlessness, indifference and failure of mental adjustment to any but simple situations.

The studies yielded no evidence of dominance in either frontal lobe.

These observations bear out the concept of a bilateral representation of personality and mental processes in the frontal lobes, comparable to the bilateral representation of muscle action pointed out by Hughlings Jackson. The two lobes are intimately connected, so that the proper function of either lobe is dependent on the transmission of impulses of a certain order and frequency through the association paths from the opposite lobe. A lesion in either lobe disturbing the frequency and type of wave discharge thus interferes with function on both sides. When, however, the irritative lesion is eliminated by lobectomy, the remaining intact lobe, freed from the influence of irregular and purposeless emanations, is able to function entirely alone and in such a way that there is practically no evidence that the opposite lobe has been removed.

DISCUSSION

DR. FOSTER KENNEDY: In listening to the paper by Dr. Stookey and his associates, one wonders why the upward cephalic urge, the neurotactic urge, has seemed, according to his results, to fail to produce any effect on the frontal lobes. The frontal lobes seem almost to be unnecessary. I can hardly think that this is true, and I am not sure that the index of human intelligence can be put, as it were, on the "subway level," on the basis of whether a person can take the right

ferry or the right bus. That hardly is enough. It is necessary to study human beings of a higher type and find out what superior attributes they lost when they lost their frontal lobes, one or the other or both. I wonder whether Keats would really have written better poetry if he had met Dr. Stookey earlier! It may be that the frontal lobe is the area in which anxiety is generated! Damage of the frontal lobes by metrazol or lobectomy induces the calm placidity of the vegetable world. However, the frontal lobes do something, and it is to be noted that the one person of intelligence in this series, the artist, said that since her operation she has not drawn, or even tried to.

DR. RICHARD BRICKNER: The paper of Dr. Stookey, Dr. Scarff and Dr. Teitelbaum is a splendid and significant contribution. Its presentation is also significant, for nothing like this has been done before with such a quantity of material and with such fulness of careful observation. The largest series of unilateral lobectomies previously described is that by Jefferson, who reported 8 cases, only 6 of which he studied sufficiently to comment on.

Some of the questions have been mentioned already in the discussion. Dr. Kennedy raised one when he said that perhaps the frontal lobes are not needed, although he did not believe it. I think that these observations lead to the conclusion that this part of the brain is not needed. It is true that unilateral lobectomy does not produce a material change in patients, even though there may be minor alterations. That has been shown before, particularly well by Dr. Stookey and Dr. Scarff. On the other hand, bilateral lobectomy changes a person completely. That must be remembered in considering whether the frontal lobes are of any use.

To me, the difference between the effect of unilateral and that of bilateral lobectomy is important because it shows something about the nature of thinking. As Dr. Stookey said, in the sphere of muscle innervation there is bilateral representation. This is undoubtedly true, particularly in regard to muscles engaged in bilateral function. I refer to muscles affecting such parts as the larynx or the jaw, in which both sides must perform at once. These are twin muscles. All such twin muscles have bilateral representation in the motor cortex. This is shown in cases of lesions of the upper motor neuron on one side. They produce hemiplegia, with paralysis of the extremities of one side, but with no, or only slight, weakening of the muscles of the jaw and larynx. On the other hand, when the upper motor neuron is injured bilaterally the consequence is pseudobulbar palsy, in which complete paralysis of all the muscles occurs.

There is an exactly similar representation as far as the frontal lobes are concerned. Remove one, and there may arise something which corresponds, at most, to weakening of the larynx or the tongue, as in hemiplegia. Remove both, and everything is gone. If one considers that fact one finds that one knows something about the anatomy of the neurons of intellect.

A great deal more could be said. I wish to mention only one or two other points. It has now been shown without doubt that there is no such thing as cerebral dominance in thinking. This has been indicated by Jefferson. It is fair to say that most of the work which has purported to show that there is such dominance and that greater difficulty in thinking occurs with injury of the left than of the right frontal lobe is not altogether sound.

On the clinical side, it has been amply demonstrated that unilateral lobectomy is a safe operation. On the other hand, when one hears that a patient with a unilateral lobectomy should have the other lobe removed, it causes one to pause.

From the facts which have been brought out tonight, one can learn another clinical point: that a frontal lesion must involve both frontal lobes if it is to give mental symptoms. It must be large enough to press on, or to shut off, the blood supply of the opposite lobe.

DR. IRA COHEN: I am entirely incompetent to discuss this paper from the standpoint that Drs. Kennedy and Brickner did. However, purely from the neurosurgical standpoint, it demonstrates two things: the skill of the operator and the

need of finer psychometric tests. While it is known that the organism has too much liver and too much kidney and that it can get along without a good part of these organs, this is the first time I know of that any one has accused man of having too much brain.

From the neurosurgical standpoint, again, justification for lobectomy may be considered under the head of the three conditions for which Dr. Stookey did it: (1) For convenience, if you will, and for safety of exposure of a tremendous subfrontal lesion. There can be no doubt in cases of a tumor of this kind that anything which contributes to the safety of the patient in the proper removal of the tumor is justified, even if it means, practically, two operations, one for removal of a part of a lobe and one for removal of the tumor. (2) For scarring. When scars are so placed that a cleaner excision is obtained by a lobectomy, it seems that the latter should be preferable to excision of the scar, which leaves in front of it a small part of the frontal lobe and a scarred field, which may in turn produce a convulsive seizure. I have always thought that in brain surgery one ought to guide oneself somewhat differently from the general surgeon. The general surgeon attempts to be most radical in cases of tumors of the most malignant type; I have always believed that the brain surgeon should put forth his best efforts in cases of the least malignant type. No matter how radical one may be, one cannot hope to cure a patient with spongioblastoma, and I believe that in a case of this type, with the diagnosis made by frozen section at the time of operation, one is wasting effort in performing a lobectomy. In cases of the less malignant type of glioma one is justified in being as radical as possible, in trying to get beyond the growth. On the other hand, time alone will tell whether a longer useful life is enjoyed by patients who have had a more radical procedure than by those who have had a less radical one.

Dr. M. H. Teitelbaum, Brooklyn: I wish to thank Dr. Stookey, as well as Dr. Scarff, for giving me the privilege of studying these cases of lobectomy from the psychiatric standpoint. The social service and the psychology departments of the Neurological Institute have contributed more than their measure to make this work worth while. The approach to the problem was many sided. It included a thorough social study of each patient before entering the hospital and subsequent follow-up studies at the homes of the patients after operation. Many such visits were made, and it was attempted to study the patients' adjustments to the various phases of life at home. Psychometric studies were made before and, in most cases, on several occasions after operation, over a variable period. Psychiatric observations were made prior to the operation, when that was possible, and afterward, and interviews were held on an average of once every month. One patient had twelve interviews, and the least number was four. In studying this problem, efforts were made to secure an all round approach, that is, from the psychiatric, social and psychometric standpoints, and the findings were evaluated as a meaningful whole. The group studied included 13 patients, 6 of whom had complete removal of the lesion; of these 6, 3 had the dominant and 3 the nondominant lobe removed. As far as I have been able to determine during this prolonged period of study, changes have not occurred in these persons. They are able to function on the same level as they were from three to ten years ago. One of the patients presented here this evening, the one who is employed in the Dugan Bakery as an inspector, is adjusted well socially, emotionally, intellectually and in every other way. He is able to carry on with life and is none the worse for his operation. There were 3 patients in this group in whom the lesion extended to other parts of the brain, and of course there is a different story. They show a definite emotional change. There is also evidence of difficulty in thinking, comprehension and attention; this study showed unquestionable changes in these persons. This is in contrast to the first group.

Dr. Joseph E. J. King: I feel sure it is understood that Drs. Stookey and Scarff were not operating on superintelligent patients. These persons had pathologic changes involving a frontal lobe, and the speakers have shown tonight the

finest group of lobectomized persons with regard to intelligence that I have seen. The persons who were demonstrated here, except for the 2 in whom some of the tumor remained, gave me the impression of having considerable intelligence. The first partial lobectomy which I observed was Dr. Cushing's amputation of the lobe to reach a lesion underneath. I have observed patients with abscesses in the right or left frontal lobe with marked destruction who after operation and recovery were well. Furthermore, in addition to tumors of the frontal lobes, of which Dr. Stookey spoke, it is in cases in which the frontal lobe has been greatly damaged and considerably destroyed, in which the patients are never normal, are ill tempered and mentally deteriorated, that lobectomy with removal of the massive scars in the frontal lobe should be performed.

DR. BYRON STOOKEY: In reply to Dr. Kennedy, I hope I did not give the impression that the frontal lobe is unnecessary, or that these persons are on a "subway level." The point concerning the frontal lobes is that, as Dr. Cohen has pointed out in another way, there is more than is absolutely needed. In considering the frontal lobes, one might compare them with a 12 cylinder engine, a V-shaped engine; either cylinder block is capable of carrying on in the absence of the other. When one cylinder block is functioning improperly, so that it throws out the other, the machine will not go, but if one takes out the offending cylinder block the automobile moves along smoothly. I wish to emphasize the point which Dr. Brickner has made, that there is no dominance, so far as we can say. We have not used the words "right" and "left," but have preferred the terms "dominant" and "nondominant"; either lobe can be amputated without showing any essential difference between the two. It has seemed to us that that is an important point in physiology, and that the problem of the function of the frontal lobe will not be solved with the primate, but with the human, brain. Dr. Scarff, Dr. Teitelbaum and I are all deeply indebted to Dr. Brickner for what I think is one of the most brilliant discussions on the functions of the frontal lobe (The Intellectual Functions of the Frontal Lobes: A Study Based upon Observation of a Man After Partial Bilateral Lobectomy, New York, The Macmillan Company, 1936).

I do not want Dr. Cohen to think that all operations for removal of the frontal lobe, to reach a subfrontal neoplasm, have been as successful as those in the 2 or 3 cases we have described. I have had a high mortality rate in this operation, and I know it is due to my difficulties in cutting down on the large blood vessels in the circle of Willis. A vessel tears close to the circle of Willis; a silver clip is put on, and the bleeding stops. While one looks at it, the vessel breaks at a new spot proximal to the silver clip and another silver clip must be put on proximal to that. The performance is repeated until the opposite side of the brain is reached, and the patient is lost in that way. I believe that with more technical skill that can be avoided some day. I now know what one is being led into, and it will take a good deal to make me put on a sliver clip again.

Dr. Scarff and I would like to make a further study of the cases of subfrontal lesions we have presented tonight. We presented these cases merely to show the magnitude of the operation. I agree with what Dr. Cohen has said, that the best efforts should be devoted to the least malignant tumors; in 1 case the most massive section was done, with Dr. Robertson's help, on a spongioblastoma. This patient did well for four or five months and then died. I am sure one's best efforts must be devoted to the least malignant tumors.

Book Reviews

Physiology of the Nervous System. By J. F. Fulton. Price, $6. Pp. 675, with 95 illustrations. New York: Oxford University Press, 1938.

This is a useful book, scholarly, thorough and timely. It is the second of the "Outlines of Physiology Series" to appear; as such it does not attempt to cover all aspects of neurophysiology, but is dedicated "to students of medicine who must bridge the gap between the concepts of neurophysiology and the problems of clinical neurology." The first eight chapters are concerned with reflexes and the spinal cord (122 pages). The brain stem is discussed in chapters 9 to 14, with the autonomic system thrown in (chapter 13). The cerebral cortex, as one would expect from the author's recent investigations, receives much attention and is given 9 chapters. The basal ganglia, the cerebellum and the nervous system as a whole each have a chapter. Bibliography and indexes, carefully prepared, round out an excellent volume. All the illustrations, 95 in number, are clear line drawings, except for the halftone frontispiece.

Three points are stressed throughout: the evolutionary principle of levels of function; the interaction between autonomic and somatic reflexes, and application of experimental work to clinical neurology and, vice versa, the contributions of clinical neurology to physiology. "Particular attention has been devoted to primate forms, since, owing to greater encephalization experimental evidence drawn from the primates is more immediately applicable to the human being than that drawn from studies of other mammals. Because it is deemed unwise to approach any phase of function without a solid background of morphology, nearly a third of the book is devoted to considerations of structure. The recent developments in neuroanatomy have been particularly stressed, notably in the domain of the receptors, the dorsal and ventral nerve roots, the structure of the synapse, the cerebellum, thalamus and its cortical projections, hypothalamus and the finer structure of the cerebral cortex. Small type has been used for the historical notes at the beginnings of chapters, for anatomical description and for controversial details, and the student may wish to postpone examination of such passages until a second reading. Each chapter concludes with a detailed summary."

The first 11 chapters are largely taken up with reflex physiology, based on Sherrington's great contributions. This is a field with which the author is thoroughly familiar, and in this 200 page exposition he expertly abstracts the important facts and brings the material up to date. Little space is given to conduction, the nature of the nerve impulse and electrophysiology (presumably because other books in the series will do this). The author is largely concerned with mammalian reflexes, emphasizing posture and locomotion. In fact, the chapter on the medulla oblongata is concerned so predominantly with decerebrate rigidity that the student is refreshingly relieved of the orthodox belief that the hindbrain was created "on old Olympus' towering tops" to confuse the student with cranial nerve nuclei and a vague "respiratory center."

The chapters on the autonomic system are important, since the author breaks with Langley, who called it a purely motor system, and decisively takes the stand that: "The autonomic is a system of cerebrospinal nuclei and tracts together with widely distributed sensory and motor nerves, ganglia, and plexuses which subserve vegetative functions of the body; in its peripheral ramifications the system is characterized by synapses in ganglia lying outside the central nervous system. The motor side of the autonomic nervous system is divided into: (i) the sympathetic or thoracolumbar autonomic, and (ii) the parasympathetic or craniosacral autonomic, this subdivision being based upon point of outflow from the central nervous system, the distribution of peripheral ganglia, and the antagonism in physiological effects on visceral tissues which in general receive innervation from both divisions." Autonomic regulation by the hypothalamus is well summarized in chapter 13. It

is a difficult feat to bring together so much recent experimental work and to evaluate it properly. Fulton states: "In addition to functional regulation of sexual activity, water, fat and carbohydrate metabolism, the hypothalamus is the primary center of heat regulation. The posterior nuclei activate the the mechanisms of heat production and conservation, while the dorsal part of the anterior group (specific nuclei undetermined) regulate the mechanisms of heat loss, including panting, sweating and vasodilatation. The hypothalamic nuclei are responsive both to reflex activation through the thermal receptors in the skin and to the temperature of the blood circulating through the region.

"Clinical syndromes of the hypothalamus are five in number: (i) *hypo*thermia (posterior nuclei), (ii) hypersomnia (posterior nuclei and mamillary bodies), (iii) the adiposogenital syndrome, with disturbed fat and carbohydrate metabolism (tuber cinereum), (iv) diabetes insipidus (supraoptic nuclei) generally accompanied by *hyper*thermia, (v) autonomic epilepsy caused by tumors, infection or intraventricular drugs with manifestations varying with the site of the lesion and involving a mixture of sympathetic and parasympathetic actions."

The chapter is helpful and worthy of careful reading, except perhaps for the paragraph on personality changes, which inveighs a bit against the psychiatrist and urges more care in the "necropsy study of the hypothalamus in the major psychoses." It is the reviewer's opinion that more normal hypothalamic nuclei should be studied before psychiatric correlations are made from observations in the few autopsies reported. Chapter 14, on the thalamus, is an equally good summary of a new field.

Chapter 15 is remarkable for its clear exposition of a difficult new field. The author was helped by Lorente de Nó, and the result is a summary of unique excellence. The neuronal structure of the cerebral cortex is described, with its cytoarchitecture and myeloarchitecture and their relation to the work of Lorente de Nó on the interaction of neurons. How misleading the laminated pictures of cells may be is shown by comparison with the true connections seen in Golgi stains and proved by physiologic experiment to be vertically arranged. "Save for layers I and II, all cortical layers contain cells having synaptic contacts with the specific afferents, so that it would be improper to call any one layer 'receptor.' On the other hand, every layer except I has axons reaching the white matter, and therefore no layer may be called the 'effector.' It is true that in some cortical fields, such as the motor cortex, a powerful efferent tract arises from pyramids in layer V; but in other fields, such as the entorhinal cortex and the occipital fields, the main efferent tracts arise from the upper layers. In every case the function of the cortex consists in stimulating distant centres, and this 'effect' is sometimes accomplished by 'association tracts' ending in other cortical fields, and again by 'projection tracts' ending in the subcortical centres. Moreover, layers V and VI are the source of powerful 'association' tracts.

"Studies on the fine structure of the cortex have revealed that, although in architectonic pictures the horizontal stratification seems to be the most important factor in cortical organization, the intracortical connections are established chiefly in vertical directions so that the whole vertical section of the cortex must be considered as a unitary system. The cortical cells are arranged in vertical chains and the architectonic layers indicate only where the bodies of cells, which are similar links in the chains, are located. But those cells, by means of long dendrites, establish connections in other layers. The elementary pattern of the postcentral-parieto-temporo-occipital isocortex is described and compared with the simpler pattern of the entorhinal cortex. It is emphasized that the pattern of the precentral, frontal, retrosplenial and limbic cortices is still unknown."

The cortex and projection systems of the occipital, temporal and parietal lobes are each given a chapter, while the frontal lobe is considered under four headings: the motor area and the pyramidal system, the extrapyramidal systems, the frontal association areas and the autonomic representation. Experimental and clinical data are brought together, and the reflex patterns of cerebral physiology are elucidated as far as present knowledge permits. No description is given of electroencephalography, nor of the more highly integrated cerebral mechanism, such as speech, con-

ditioned reflexes and learning; in fact, anything so complex that it might be termed "psychological" has been purposely omitted.

In a book which discusses and summarizes many controversial subjects the author of necessity makes many statements which do not please all readers. Occasional lapses in clearness mar the text. For example, in the difficult chapter on the cerebellum (page 530), it is said of tremor: "If present during rest, it arises only in those attitudes which must be maintained by volitional effort." Again, on page 522 is the statement: "The 'unitarian' concept of cerebellar function, nevertheless, has pointed to a type of *functional* as opposed to an anatomical localization," followed ten lines later by the statement that "the anterior lobe, through its spinocerebellar afferents and rubrospinal efferents, is equipped to preside over postural mechanisms. Comparative studies also indicate that the flocculonodular lobe is equipped to influence vestibular mechanisms, the pyramis undoubtedly has some connection with organization of vision, and that the neocerebellum is concerned with the integration of volitional movement—all highly integrated functions and not anatomical entities." To the reviewer it seems that there can be no opposition between function and structure; any structure in action has function, and any function must be the product of anatomic entities. As for the cerebellum, Fulton describes functions for the anterior and the flocculonodular lobes and the neocerebellum (page 541). Since the cerebellum is divided symmetrically, with largely homolateral control over the right and the left side of the body, the resulting anatomic localization for a small organ seems to be fairly well outlined.

It is difficult to correlate the statement on page 113: "In nearly all muscles of the human body some red fibres can be detected" with the sentence appearing on page 115: "All physiological flexor muscles are made up of pale rapid fibres —red fibres being found only among the (single joint) physiologic extensors." That "lesions of the body of Luys give rise to hemiballismus" is one of the few well substantiated facts about the basal ganglia, but that the movements should be described as "coarse choreiform" (page 500) is doubtful. More exact definitions of the terms "spasticity," "rigidity" and "tonus" are needed to make clear the discussion of the physiology of the basal ganglia (pages 501 to 506). It is difficult to understand how lesions of the substantia nigra cause "rigidity" and those of the red nucleus "spasticity," nor does the reviewer know of any proved cases of "isolated lesions of the substantia nigra"; moreover, he believes that lesions of the body of Luys do not cause symptoms "similar though less conspicuous." But this is a difficult field, with much conflicting evidence; the author should not be nagged, but should be complimented for doing a difficult job effectively. The book should be in every neurologic or psychiatric library. Indeed, medical students, to whom the book is dedicated, will really learn something about the nervous system if they discard conventional textbooks of anatomy and read Fulton's instead.

Le groupe des psychoses hallucinatoires chroniques. By Charles Henry Nodet. Paper. Price, 40 francs. Pp. 164. Paris: Gaston Doin & Cie, 1938.

In this essay Nodet proposes to criticize the nosologic position of the "chronic hallucinatory psychosis," a clinical syndrome which has long played a unique and significant role in French psychiatry. The essay is prefaced by Henri Claude, who welcomes not only the critical reorganization but the emphasis on structural and dynamic psychopathologic doctrines which are the basis of the criticism.

The essay is divided into three sections. An introduction serves to present the significant historical background of this syndrome in French psychiatry and to explain its relationship to the evolution of the concept of chronic delusional states. The second section deals with a direct criticism of the syndrome from clinical and theoretic points of view. From a clinical point of view the author offers the following arguments: (1) It is difficult to differentiate exactly hallucinations, interpretations, illusions and intuitions, as they are frequently intermingled. (2) A study of all the patients (37) in the same service of the hospital who were admitted before 1930 and whose condition had been diagnosed as "chronic hallucinatory psychosis" leads to the conclusion that the delusional structure differed consider-

ably and could not be superposed. (3) The evolution in the 37 cases was so polymorphic that it could not serve as a common bond in the individual cases.

Thus, the unity of the "chronic hallucinatory psychosis" is not justified by the symptomatology, structure or evolution of the psychosis. In the preceding argument the author has included well written reports of the 37 cases included in the series.

From a theoretic point of view the author finds it difficult to conceive of a hallucination producing a delusion. He favors a dynamic conception of the hallucination in considering it as a functional dissolution in the sense of Hughlings Jackson. Nodet believes that a hallucination is an erroneous belief in the perception of self and in the perception of the external world. Its nature is phenomenologically sensory, but pathogenetically illusional. The hallucination is fashioned from the personality of the subject. It is an integral part of the total behavior, but is secondary to the delusional structure. The hallucination is a primitive means, although not a necessary one, through which a patient may express his delusional content or reveal his emotional life. It is a superstructure of characteristic and irreducible material, but its basis is the structure of the personality.

In the concluding section of the essay the author attempts to reconstruct the chronic delusional states from a structural point of view. He defines the delusional structure as an aggregate of the difficulties experienced by the patient in proportion to his capacity. He states that it is a characteristically assembled psychopathic state. All transitions from one structure to another are then ideally possible and practically realized, as in the comparison of many psychoses with each other or in the historical unfolding of the same psychosis. The classificatory divisions he chooses are the delusions of paranoiac structure, the delusions of paranoid structure and the delusions of paraphrenic structure. In this section the author has not deviated markedly from the classification introduced by Kraepelin in his textbook (Psychiatrie: Ein Lehrbuch für Studierende und Aerzte, ed. 8, Leipzig, J. A. Barth, 1909-1913). The latter created a group — paraphrenia — which included dementia paranoides, formerly classified under dementia praecox, and certain other paranoid states which do not show the reorganization of the personality and the defects of affect and thought characteristic of dementia praecox. The main disturbance is intellectual. This group occupied a midposition between his paranoia and the paranoid types of dementia praecox. He subdivided paraphrenia into four divisions, viz., paraphrenia systemica (which resembles the paranoiac structure outlined by Nodet), paraphrenia expansiva, paraphrenia confabulans and paraphrenia phantastica. Nodet's second division includes the hebephrenic and paranoid forms of dementia praecox and the paranoid psychoses. The latter are related to Kraepelin's paraphrenia expansiva and paraphrenia phantastica. In his third group Nodet describes a syndrome, free from the schizophrenic process, characterized by imaginative, hallucinatory and superstitious reactions, which may at one time have been classified as chronic mania, postmelancholic delusions or paranoid states in other psychoses. He included these reactions in his concept of paraphrenia.

Clinically, it is important that Nodet has demonstrated the relationship between the "chronic hallucinatory psychoses" and the more familiar clinical syndromes which have come from the classification of Kraepelin. In Nodet's survey he found most of the patients experiencing the paranoid type of dementia praecox, although some were to be found in the group with paranoia and others with paranoid states.

The author criticises the conceptual basis of the "chronic hallucinatory psychosis." He demonstrates adequately the heterogeneity of the symptomatologic, structural and evolutionary aspects of this syndrome. He points out the relation between this syndrome and the paranoid, paraphrenic and paranoiac forms of delusional structure. In this he has achieved a coherence long needed in French psychiatry. The attention devoted to an appreciation of the fundamental personality matrix of the patient, as well as the symptoms and course of the illness, emphasizes the importance of modern psychopathologic doctrines in the understanding of the patient.

More than this, Nodet presents a historical review of the work of various German and French clinicians concerned with the mechanism of the hallucination. Before Nodet, Claude had criticized the assumptions of de Clerambault, Meynert, Nissl and others, who held that the hallucination was of organic origin and wholly explicable without knowledge of psychogenic factors. Freudian concepts have aided inestimably in the understanding of the evolution, content and purpose of the hallucination. But as yet little is known of the actual mechanisms, physiologic or psychologic, which cause the sense deception.

A Bibliography of the Writings of Harvey Cushing Prepared on the Occasion of His Seventieth Birthday April 8, 1939. By the Harvey Cushing Society. Price, $5. Pp. 108. Springfield, Ill.: Charles C. Thomas, Publisher, 1939.

On April 8, 1939, the Harvey Cushing Society, holding its annual meeting in New Haven, Conn., celebrated at formal dinner the seventieth birthday of its senior patron and guest of honor, Harvey Cushing, which occurred on that day. Every member not incapacitated by illness or other urgent cause attended, and congratulatory messages from all over the world, beginning with the "Chief's" co-father-in-law, the President of the United States, were read. Dr. Cushing was then presented with this book, which had been prepared unbeknownst to him. Its foreword had best be repeated.

"The present compilation includes all of Dr. Cushing's published writings that could be traced through the usual bibliographical channels. The first section sets forth his degrees and titles, the second his books and monographs, and the third is a chronological list of his contributions to periodicals extending over a period of an even forty years; the final section is an alphabetical list of papers which have emanated from Dr. Cushing's Laboratories and Clinics. The section on books contains 13 separate titles, with a total of 24 entries, including separate editions and translations; in the list of journal contributions 306 titles are represented; and, finally, 328 papers have been cited that Dr. Cushing has himself encouraged or directed. In offering this bibliography to him on his birthday, we do so in the hope that his extraordinary productivity may long continue, and that, by making his writings more readily available, others may derive the enduring inspiration that we have had from his precept and example.

"The Society takes this opportunity of expressing its gratitude to Mr. Carl Purington Rollins, Printer to Yale University, for the time and attention he has given to designing the bibliography. It will no doubt interest readers to learn that the type face, well known to typographers as 'Cushing No. 25,' was originally introduced by Josiah Stearns Cushing, a distant kinsman of Harvey Cushing. To the George Banta Publishing Company which has printed the bibliography, and to Mr. Charles C. Thomas who will publish it, the Society is also greatly indebted."

This edition has been prepared for sale, and well might it be obtained and pondered over by any neophyte who aspires to glory.

L'electro-encéphalogramme normal et pathologique. By Ivan Bertrand, Jean Delay and Jacqueline Guillain. Paper. Price, 90 francs. Pp. 293, with 94 figures. Paris: Masson & Cie., 1939.

The field of electroencephalography is now so diffuse that a well written monograph containing not only an extensive bibliography but also a well illustrated discussion of fact and theory is doubly welcome. The textual material (as up-to-date as an ever widening field allows) surveys the electroencephalogram of animals and man, normal and pathologic, in clinic and in laboratory.

A brief historical introduction is followed by details of apparatus and methods. The ink-writing oscillographs are rather summarily dismissed in view of the valuable contributions made with them (covered in the text) and their convenience of yielding immediately available records. Figures illustrating potentials evoked

by sensory stimuli, especially visual, are deficient, and this section is, therefore, less complete than those on sleep, anesthesia and psychic disorders. The latter also contain most of the authors' original work. Cerebellocerebral relations and epilepsy and other involuntary movements are treated under motor activity. The parts devoted to localization and architectonics present both sides of controversial problems (often uncritically, however, as in the case of the occipital origin of alpha waves). A section on localization of cerebral disorders by the electroencephalogram follows. Factors which influence brain waves in experimental animals and spontaneous rhythmic activity and synchrony in brain and peripheral nerves are briefly considered. Particular emphasis is laid on closed circuits between the thalamus and the cortex.

The book is well printed, though paper covered. The extensive references suffer from minor inaccuracies in copying English names and extracts, and they are frequently unidentified in the text by date of publication. More serious deficits are the omission of time and voltage calibrations from the authors' figures and the inadequate identification of specific figures by text references. There is no index, but this is partially compensated for by the extensive subheadings in chapters. The volume offers a highly usable review of this field of growing clinical importance, and its value as a reference work is enhanced by the close apposition in the text of English and German idioms to their French equivalents.

The Common Neuroses, Their Treatment by Psychotherapy: An Introduction to Psychological Treatment for Students and Practitioners. By T. A. Ross, M.D., F.R.C.P. Second edition. Price, $4. Pp. 236. Baltimore: William Wood & Company, 1937.

Probably one of the greatest difficulties encountered by the psychiatrist who is called on to give to the medical student the requisite general knowledge of psychiatry is to know what to teach and what to omit. The ever present danger is that he will try to teach too much and succeed only in confusing his pupils. In this excellent book, which has been largely rewritten in this, the second, edition, the problem of a simple and yet adequate selection of material has been ably handled. The prime purpose of the author has been that of providing a simple and intelligible account of the common neuroses, treatment for which not only can but must be carried out by the general practitioner if the patient is to receive treatment at all. At the same time there is emphasis on the fact that "there is a residue which the general practitioner will be well advised not to touch." While paying tribute to the contributions of Freud, the author has, wisely in the opinion of the reviewer, avoided any attempt to expound psychoanalytic views and has eliminated a chapter dealing with this topic which was contained in the first edition. The views expressed are founded largely on the teaching of Dejerine and are adequately documented with case material. Study of the book will amply repay the physician in any field of medicine and should do much to lay a foundation for a more general appreciation of the meaning of psychiatry. The book can be recommended highly as an aid in teaching undergraduate medical students.

A Text-Book of Mental Deficiency (Amentia). By A. F. Tredgold, M.D., F.R.C.P., F.R.S.E. Sixth edition. Price, $7.50. Pp. 556, with 34 illustrations. Baltimore: William Wood & Company, 1937.

The sixth edition of this well known and widely accepted textbook, the first edition of which appeared in 1908, lives up fully to the excellence and quality of earlier editions. The material has been enriched by the inclusion of much information that has been developed during the nine years that have elapsed since the fifth edition was published. The book remains the outstanding publication on the subject in the English language and cannot be too highly recommended as a basis for an orderly presentation of the forms of mental defect.